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THE BOWMAN LECTURE

ON

SOME HEREDITARY DISEASES OF THE EYE

BY

E. NETTLESHIP

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BEING

THE BOWMAN LECTURE,

Delivered on Thursday, June 10th, 1909,

BY

E. NETTLESHIP.

INTRODUCTORY.

I HAVE chosen the heredity of certain diseases of the eye as my subject, because whilst possessing great attractions, it furnishes a theme upon which one who is to some extent out of touch with the newest clinical ophthalmology may still, perhaps, hope to speak without presumption. I believe also that all here who had, like myself, the great privilege of acquaintance with Sir William Bowman, of experiencing the charm of his voice and diction, and of seeing him at work, will agree that had he been alive to-day he would, with the keen but discerning enthusiasm that he always brought to bear upon new scientific problems, have recognised that the study of heredity confronts us with subjects of absorbing interest, the right interpretation of which must have important consequences for the future of our race. As a matter of fact Bowman actually communicated to Charles Darwin some of the earliest generalised observations upon the heredity of cataract, and, as we shall see further on, later work has but confirmed his statements.

Taking a few of the principal ophthalmic diseases, the hereditary transmission of which is now recognised, I propose to-day to consider them from that point of view,

and at the same time to indicate some of the directions in which further reseach into their nature is most needed. Many, such as the heredity of errors of refraction and of the musculature of the eye, I cannot touch. We could all cite plenty of examples showing the family prevalence of both these classes of defect, but I do not think much has yet been done in the direction most suitable for clinical observers—the careful record and analysis of individual pedigrees. The elaborate statistical enquiry upon the inheritance of ametropia lately brought out by Professor Karl Pearson and Miss Amy Barrington* will help to elucidate the ever-present problem of environment *versus* heredity in the causation of myopia, although the imperfection of the data (data derived from ophthalmological examinations, be it confessed) often detracts from their value to the biometrical statistician.

I shall say but little on the theoretical side of my subject, being, as I am, quite unable to deal with the biological and mathematical complexities in which the modern student of heredity finds himself involved. As one who must be content with a very modest share of spade work I am grateful that in the medical domain there is still virgin ground where the tasks of excavating, collecting and recording may be safely undertaken by those who enjoy them. And here I wish to express my deep indebtedness and cordial gratitude to the many colleagues and friends who have generously furnished me with cases and numerical records bearing upon heredity, and have, often at much tedious trouble to themselves, aided me in the collection and disentanglement of genealogical details. I could have done next to nothing without such help.

Before getting to close quarters with individual diseases I must ask your indulgence whilst, in order to avoid needless repetition, I refer to certain generalities.

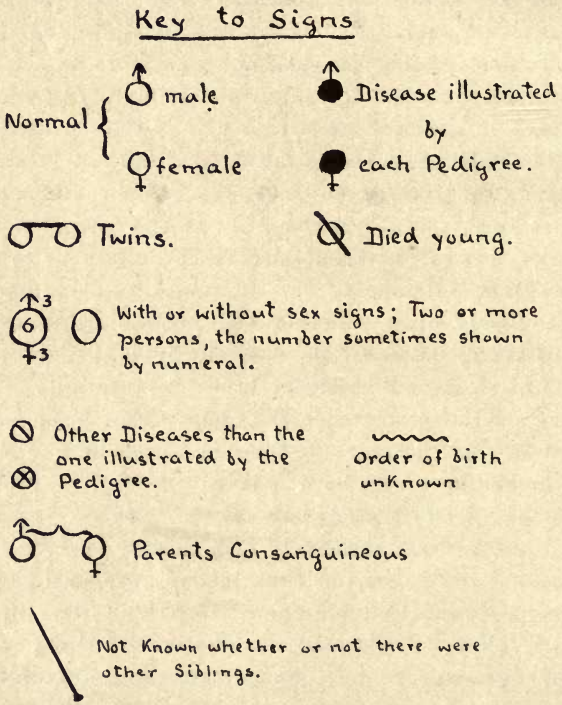
* "A First Study of the Inheritance of Vision and of the Relative Influence of Heredity and Environment on Sight." By Amy Barrington and Karl Pearson, F.R.S., *Eugenics Laboratory Memoirs*, v, 1909. London: Dulau and Co.

One of the first questions generally raised when heredity is under discussion is the influence of consanguinity in the parents or ancestors. The belief that kinship between parents is a source of disease or degeneracy in the children is widely spread and has its roots deep in the past; and yet we meet every day with marked differences of opinion and practice in regard to the matter, between one house or family and another. The real question is this: Can the marriage of blood relations produce disease of which neither the parents nor ancestors showed any trace, or does the consanguinity operate simply by increasing the likelihood that both of a pair of parents will contain the seeds of the same undesirable, or it may be desirable, character? If the former be true no cousin-marriage can be said to be safe. But if the latter be the correct position —and the results of all modern research appear to point that way—the outcome of the consanguineous union will depend entirely upon whether the particular disease, or other heritable character, is carried by both parents, by only one of them, or by neither; the consanguinity will be operative only if it increase the chance that both parents are tainted. If the transmissible condition be one that is very common there may be as much chance of its presence in both of an unrelated pair as in both of a pair of cousins; but any comparatively rare disease is more likely to be present in two cousins than in two unrelated persons.

Accordingly we find a general belief in the medical profession that in diseases so relatively infrequent as retinitis pigmentosa and deaf-mutism consanguinity of the parents plays an important part. And the same is true of some other conditions where, as in the diseases just named, both sexes are liable to suffer from, and both liable to transmit, the disease.

But in sex-limited conditions, such as Leber's disease and congenital colour-blindness, where only the males suffer, though the disease is carried down by (apparently) normal females, consanguinity of parents is known to be infrequent. If we start with a colour-blind male we know

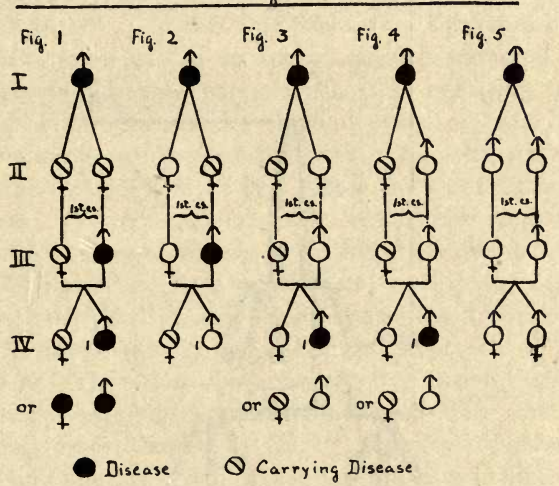
that all his children will, as a rule, have normal colour-perception; that if his sons, who neither exhibit nor carry the defect, have issue, that issue too will be normal; but that some of the sons of some of his daughters will show the defect, whilst the other daughters, who we presume do not carry it, will have all normal children. If one of these normal children of a normal daughter marries a cousin,



the issue of one of the normal sons, the result, as regards colour-perception, will be the same as if two unrelated normals marry. In fact, if the sex-limitation were invariable in colour-blindness and other sex-limited conditions, only one kind of cousin-marriage out of the several possible kinds shown in Figs. 1 to 5 (I speak of first cousinship throughout) would be attended by special risk, *viz.*, when the mothers of the parents are sisters who,

although not manifestly colour-blind, both carry the defect (Fig. 1, II). If one of these two grandmothers of the male IV, 1 is free from taint (as in II, Figs. 2 and 3), it is impossible to understand that she can have any more influence than if she came from a different stock; and the same will be true if one or both of the two grandparents (parents of the cousins) be male and unaffected (II, Figs. 4 and 5).

In this connection Fig. 48 (Leber's disease, a sex-limited affection; Klopfer's case, 1898), is instructive.



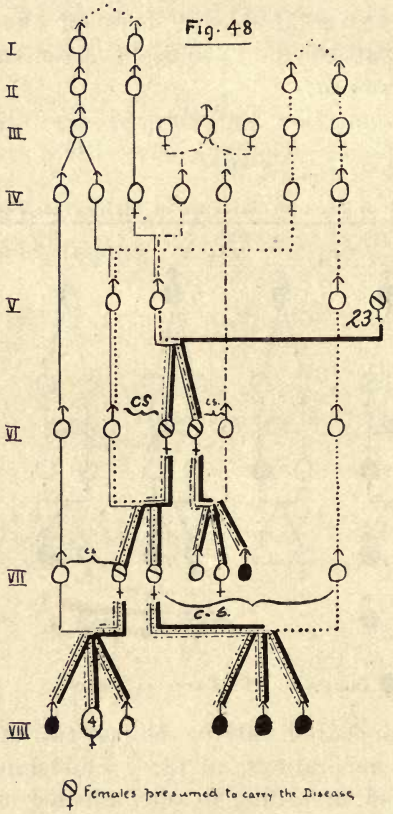
The disease appeared only in the last two of the eight or nine known generations, in three childships cousins to each other, and, according to rule, affected males only.*

Each of these childships was the issue of a consanguineous marriage; but, as the lines show, these parental cousinships all came from *grandfathers* who were unaffected, and therefore, on the hypothesis, did not contain the disease. If the normal rule obtained, as seems to have been the case, the disease must have followed the thick, black line to an affected male

* Some particulars of this pedigree will be found at p. CVIII.

ascendant of V, 23, in which case the cousinships do not count, for V, 23 was from an outside stock.

But limitation of the disease to the males and transmission through normal females is not invariable. For



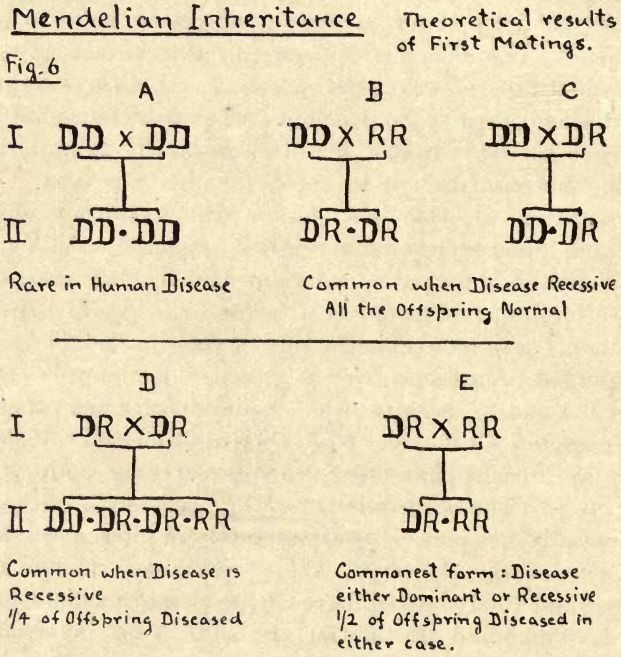
though I believe that an unaffected male never carries colour-blindness, exceptions are found to the other part of the rule. Thus an affected male sometimes transmits to his son, and colour-blindness is sometimes seen in females. The influence, whatever it is, that usually prevents the colour-blind male from passing the defect on to, or through, his sons and compels him to transmit it only

through daughters who do not themselves show it, is sometimes lacking.

The effect of consanguinity and the facts as to sex-limitation can both be considered in relation to the Mendelian theory. According to this theory of inheritance, a character and its opposite or absence is represented in the gametes by particles; this at least applies to certain characters, pathological as well as physiological. These particles occur in even numbers or pairs in each gamete. The members of each pair may be similar (both representing presence of the character, or both representing its absence), or may be dissimilar (each pair containing one of each kind). In the fertilised germ the pairs derived from the gametes, so to speak, change partners. The constitution of the particles in the resulting zygote depends upon that in the original gametes; the zygote may contain only pairs representing the character, only those for its complement or absence, or a hybrid between the two. For convenience, one of the characters (or its particulate representative) is called "dominant" (D.D., Fig. 6 A and B), because when it unites with the other, or "recessive" (R.R., Fig. 6 B), the resulting hybrid shows only the former character, although carrying both (D. R., Fig. 6 B). The other character, the "recessive," although potentially present, is undeveloped and does not show. In some cases, however, the "recessive" factor does show, and then the visible result is an intermediate form. As I understand the matter, the vital point in Mendel's interpretation of the facts of heredity is the separate, and numerically equal, particulate representation of qualities in the gametes. Visible dominance is not an essential part of the theory, because intermediates occur showing both the constituent qualities. The terms "dominant" and "recessive" are convenient and useful, but must be dissociated from any conception of what may be either "good" or "bad," "desirable" or "undesirable," "strong" or "weak"; indeed, as we shall see presently, in some cases the disease or defect behaves as what Mendel

called a dominant over the normal condition, in other cases as a recessive. But since the victims of the same hereditary disease, be it purely dominant or purely recessive, scarcely ever intermarry, no trace of pure disease is established.

In most cases, using Mendelian terms, an hereditary disease is transmitted by the mating of an impure, or hybrid, dominant (D.R.) with a recessive (R.R., Fig. 6 E),



and if sufficiently large numbers be taken half of the resulting offspring should be normal and half diseased, whether the disease be the dominant or the recessive partner.

If the disease be dominant it is of course rare for mating to occur between two persons suffering from it. When such union does occur all the offspring should be diseased if the dominance in one parent or both be pure (Fig. 6 A, B, and C), three quarters if both parents be hybrid dominants (Fig. 6 D).

If the disease be recessive the matings shown in C and D will also be frequent, for then either one parent or both will appear normal; mating C will give only normals, but half of them should carry the disease; in mating D one quarter of the offspring should show the disease if sufficiently large numbers be taken, and one half should carry it invisible or potential; in mating E, as just stated, the disease should appear in half and be carried by the other half, if sufficient numbers be taken.

Therefore if the simple Mendelian theory be applicable to any human disease or defect we shall expect that, in most cases, either one quarter or one half of the offspring will show the condition (Fig. 6 D and E).

The assumption is that dominance and recessiveness are constant for the same character in all stocks and families; that the same character or disease cannot be dominant in one pedigree and recessive in another. But when a given character is linked with sex in such a way as to be manifest only in one sex (the male), although carried in an incompleted and invisible state by the other (female), the fact has been explained in Mendelian terms by Professor Bateson on the assumption that the character, although dominant in the male, becomes recessive in the female. This hypothesis appears to explain some otherwise difficult cases. For example it can be made to account for the clinical fact—invariable as far as we yet know—that a colour-blind woman transmits her defect to *all* her sons, and that she herself has always had a colour-blind father. But on the other hand it does not explain the ordinary experience that a colour-blind father very seldom has colour-blind sons.

And in many other cases the experimental breeding of plants and animals has given results which, in order to bring them within the four corners of the Mendelian theory, require the assumption of various modifying or controlling influences. But this is not the time, nor am I the person, to discuss the hypotheses dealing with such subjects as "dihybridism," "gametic coupling," "rever-

sion on crossing," "epistatic" and "hypostatic" factors, and the complex results that flow from them, results in which the actual and the expected numbers are often so strikingly near.

Whether the Mendelian theory, or any one of the current doctrines of heredity, contains the whole truth is perhaps doubtful; but we may rest assured that sooner or later a ground will be discovered upon which the advocates of the various theories can meet in common. Meantime, I conceive that our contribution to the problem, as students of the natural history of living man, should consist in the collection, classification and analysis of fresh pedigrees of disease or defect wherever we can find them.

The Mendelian theory in its simple form is so precise, and in regard to a number of unit characters in certain plants and animals its expectation has been found to fit so nearly with experimental results, that no surprise can be felt at the attraction it has for workers in human heredity. But, founded as the theory is upon a strictly quantitative conception, it would certainly never have been formulated from data afforded by human disease alone, and this for several reasons. Thus it is difficult and often impossible to get a record of all the maternal conceptions; and even then we do not know how many of the miscarriages and stillbirths, and but rarely how many of those born alive but dying in infancy, would have been affected.* Again, when dealing with a condition that comes on many years after birth the record is incomplete unless all can be followed quite up to the susceptible age. Then it is, to say the least, probable that in some cases the disease which exists potentially may never appear for lack of some agent or influence—called for want of a better name an excitant or stimulant—that is necessary to complete it, *e. g.* Fig. 38, retinitis pigmentosa probably brought out

* We can at present only assume that had these immaturities and early deaths survived they would have suffered in the same proportion as those who lived. This assumption, however, may be unwarranted.

by hæmorrhage. Further, there can be little doubt that in certain cases we have to deal with equivalent, substitute, or heteromorphic diseases—cases in which the same cause produces disease of one part, *e. g.* the retina, in one person and of another part, *e. g.* the organ of hearing, in another member of the same genealogy. In popular no less than medical belief such heteromorphism is sufficiently notorious in the case of gout, though the evidence is somewhat lacking in precision. Lastly, can we regard it as certain that single births, occurring at comparatively long intervals, always follow the same laws of transmission as frequently recurring multiple broods?

Amongst *normal* human characters the colour of the iris has been investigated, and Hurst has shown that pigmentation is in Mendelian terms dominant to lack of pigment, *i. e.* the brown or otherwise pigmented iris is dominant to the pure blue or grey iris. Captain Hurst* was good enough to let me see, on May 17th last, at the Village School at Burbage, his home in Leicestershire, a considerable sample (thirty-eight) of the persons upon the colour of whose irides his paper was based. I wished particularly to know whether entire lack of visible pigment meant the same thing to myself as to Mr. Hurst. Mr. Hurst's method is to examine the iris with a magnifier out of doors in good daylight. The ones I saw were all children attending the school and we examined them in the open yard outside at about 2 o'clock. In those that Mr. Hurst had recorded as "simplex," *i. e.* entirely free from visible stroma pigment, I could find not the least evidence of pigment in any, except a doubtful slight trace at one part of one iris in one child, so slight that I thought the appearance might perhaps be due to the colour of an unusually large blood-vessel. In the slightly and partially pigmented ones Mr. Hurst's observations and mine were also in complete agreement; in many of this class the pigment, although very evident on careful scrutiny

* Hurst, C. C., "The Inheritance of Eye-Colour in Man," *Proc. Roy. Soc.*, B., lxxx, 1908.

at close quarters, was invisible to casual inspection and the colour of such irides would undoubtedly have been passed as "blue" or "grey," meaning "devoid of stroma pigment," if examined without a lens, or at a distance of twelve or more inches, or in a not very well lighted room.

In regard to human *diseases* and *defects* I consider that, in spite of, or allowing for, numerical discrepancies that must occur from such causes as have been mentioned, many pedigrees are, in their broad features, *consistent with* Mendelian theory. I purposely use no stronger term; for although, as I have said, human pedigrees do not, and cannot, prove the theory, we may well be interested in finding that some of them are at least compatible with it so far as they go. Pedigrees abound in which the rule, "once free always free," required by Mendelism for a dominant disease is found to hold good; and others occur in which the frequency of consanguineous marriage and of discontinuity in transmission are consistent with a recessive. It is when we come to *quantities* that the relative numbers of diseased and normal are often found to be wide of the mark, sometimes far too many, sometimes not nearly enough, being affected. In regard to such discrepancies we may remember, besides the hindrances to complete knowledge above mentioned, that at present we know very little about the indications and measure of inherited *liability* or *soil* as distinguished from actual disease, *e.g. liability* to tubercle or to mental disease; nor do we know whether in certain cases death in infancy may not itself take the place of the disease that is to appear later in life in the survivors.* Then, again, granting exact numerical segregation of unit characters, it seems reasonable to expect, for man and the higher animals,

* For a case in which D.R. × D.R. gave, in self-fertilised variegated antirrhinum (snapdragon) 2 instead of 3 D. to 1 R., because the remaining fraction died for want of chlorophyll during germination, *see* Baur, quoted by Bateson in his *Mendel's Principles of Heredity*, 1909, p. 253, where, under the heading "Departures from Numerical Expectation," other facts and suggestions bearing on the subject will be found.

complexities due to interaction far more intricate than any yet dealt with in experimental biology. Finally the particulate representatives of hereditary *disease* must often, if not always, be far less ancient in origin than those representing normal charcters, and therefore presumably more easily modified by disturbing influences during embryonic life.

Even the term "unit" needs to be defined, for just as hardly any two persons are exactly alike even in a single normal feature, and as in cases of family disease or defect minor differences can often, perhaps generally, be observed between the morbid appearances in one or another of the affected members, so we can safely take it for granted that the germinal representatives differ slightly amongst themselves in some of their attributes. The alternative would be to suppose that all slight variations of inherited condition were due to environmental causes either before or after birth.

I propose, nevertheless, to give, for what they may be considered to be worth, the numbers of affected and normal actually found in the collected pedigrees of a few of the diseases we are concerned with to-day, for comparison with Mendelian expectation.

Only those sibships (childships) were used that were probably complete, and either contained a case or cases of the disease or were the offspring of an affected parent. Early deaths, stillbirths and miscarriages have been omitted, as well as all sibships that were certainly, or even probably, incomplete. When the disease was discontinuous the intervening (free) generation was not counted. All these omissions, though making for accuracy, entail large deductions from the total.*

I. Acquired or post-natal cataract at all ages. Descent continuous: total 440 (100), affected 177 (40), normal 263 (60), numbers that are quite wide of Mendelian requirements. But we may assume without the least hesitation that had every member been examined

* The data used are given in Appendix I.

incipient senile cataract would have been found in some, perhaps a fair number, of those who, judging only from report, have been entered as normal; the 40 per cent. is therefore too low, though we cannot say by how much.

II. Congenital cataract of all kinds. Descent continuous: total 566 (100), affected 260 (46), normal 306 (54), a bad approximation to the equality required by the Mendelian scheme, Fig. 6 E, if the pedigrees used are as complete as they are supposed to be.

III. Retinitis pigmentosa; pedigrees showing continuous descent only: total 387 (100), affected 198 (51), normal 189 (49). Practical equality as in Fig. 6 E.

IV. Congenital night-blindness with continuous descent. For quantitative purposes the great Cunier pedigree is too inexact for this purpose. Other data give: total 63, affected 33, normal 30. Not far from equality, as required by Fig. 6 E.

V. Leber's disease. Descent discontinuous, all cases, female as well as male, being counted: total 547 (100), affected 245 (45), normal 302 (55). A poor approach to equality.

It must, however, be mentioned that in this disease the proportion of diseased to normal is influenced by sex.

(*a*) In families where the disease affects males exclusively the numbers are—total, both sexes, 402 (100), affected males only, 165 (41), normal, both sexes, 237 (59).

(*b*) In families where the disease affects some females as well as males the numbers are—totals, both sexes, 145 (100), affected, both sexes, 80 (55), normal, both sexes, 65 (45).

VI. Retinitis pigmentosa; pedigrees showing invariably discontinuous descent.

The numbers in this group can be interpreted in Mendelian terms on the assumption that the disease is dominant in some sibships and generations, recessive in others.

The totals are small, but may, for the present, be analysed into three sub-groups as follows:

(*a*) Seventeen completed sibships containing—total 117 (100), affected 55 (48), normal 62 (52).

(*b*) Ten similar sibships containing—total 58 (100), affected 15 (26), normal 43 (74).

(*c*) Three similar sibships, containing—total 13, affected 11, normal 2.

It will be noticed that in these three small sub-groups, where in all cases the parents were normal, only the second (*b*) fits the Mendelian expectation of Fig. 6 D, where two impure dominants carry the disease as recessive and throw one quarter of their offspring diseased. Both (*a*) and (*c*) require dominant to have changed place with recessive in the second generation in order to bring them into the theory at all. (Fig. 6 A and C.)

The numbers I have just quoted are the outcome of careful examination and the exclusion as far as possible of incomplete examples; I hope, therefore, that they will not be without interest at the present time. I may say that I was quite unprepared for such a near approximation to halves and quarters as are shown by certain of these groups.

Allusion has been made to the change of dominance supposed to occur in sex-limited disease. I believe there is clinical ground for suspecting that dominance, if we use the term, may sometimes change, or rather may be different, for the same disease in different families irrespective of sex; and if this be true, the factor causing the alternation of dominance in the sex-limited cases may be, not sex itself, but something else, usually, but not invariably, associated with sex. Retinitis pigmentosa, for instance, appears to be recessive in many families, but in the largest recorded pedigrees it behaves as a dominant, and yet it is the same disease in both instances. If such change can occur at all, we need go only a step further in order to explain the first appearance of a dominant disease. A condition that has for want of meeting with another similar gamete been propagated for generations as recessive in an impure dominant would at

once become apparent, *i. e.* dominant, if it came under the action of the supposed transforming influence.

I now leave these crude speculations and come to the safer ground of observation.

Anticipation in hereditary disease means the manifestation of the morbid change at an earlier age in each successor, either in members of each succeeding generation as a whole, or in successively born children of one parentage. Bowman was one of the first to notice anticipation in successive generations in hereditary acquired cataract,* and examples of the phenomenon will be quoted later. It is only seen in some of the families, and we do not yet know in what proportion of them.

Anticipation in generations is also a marked feature in hereditary glaucoma, but the material hitherto collected is smaller than for cataract.

Anticipation is also seen fairly well marked in connection with Leber's disease, both in successive generations and successively born siblings.

Anticipation is not known to occur in retinitis pigmentosa, and I believe has not been proved in the now well-known hereditary reticular and nodular keratitis.

This anticipation in heredity is by no means peculiar to diseases affecting the eye. It appears to occur in phthisis,† and is certainly sometimes met with in hereditary diabetes (Fig. 7),‡ and hereditary jaundice with enlarged spleen (Figs. 8 and 9)§; also in at least one

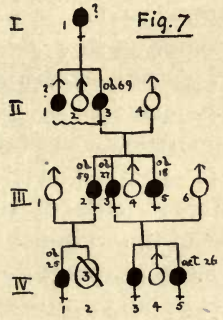
* Bowman communicated these observations to Darwin, who incorporated them in his chapters on "Inheritance" in *Animals and Plants under Domestication*, i, p. 453, and ii, p. 56 (1868). They do not seem to have been published in any other form.

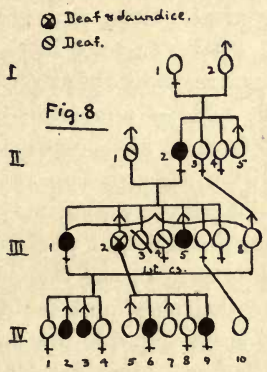
† Pollock, J. E., *Medical Handbook of Life Assurance*, 4th edition, 1895. Karl Pearson, *A First Study of the Statistics of Pulmonary Tuberculosis*, 1907. (*Drapers' Company Research Memoirs: Studies in National Deterioration*, ii.)

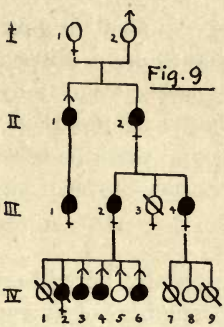
‡ The ages at death are given in Fig. 7 (unpublished case, E. N.), but they could not be conveniently inserted in Figs. 8, 9 and 10.

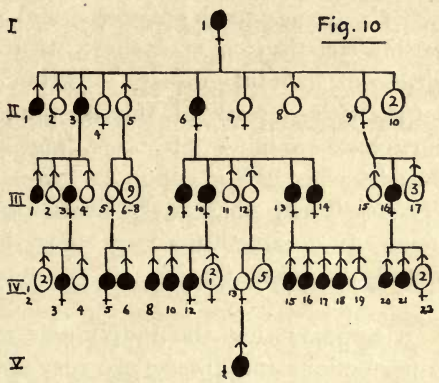
§ Figs. 8 and 9 are constructed from the paper, "Some Cases showing Hereditary Enlargement of the Spleen," by Claude Wilson, *Clin. Soc. Trans.*, xxiii, 162 (1890), and xxvi, 163 (1893).

extensive pedigree of hereditary ataxy* (Fig. 10), and possibly in some of the other chronic diseases of cord and brain. When a disease tends always to occur at a later age in one sex than the other, the comparison as to anticipation in hereditary examples must of course be made between members of the same sex.









It appears to me that the subject of anticipation deserves much more attention than it has received in relation to theories of heredity and to the origin and extinction of heritable conditions.

We may note that the reverse process, appearance of the disease at a later age in the later born, though

* Sanger Brown, *Brain*, xv, 1892, p. 250, and xx, 1897, p. 276.

sometimes taking place irregularly in successive siblings, does not seem to occur in successive generations.*

Two different heritable conditions may be met with in the same pedigree, and care is then necessary to distinguish coincidence from correlation or equivalence. Thus in Fig. 11 we have congenital lamellar cataract, congenital ptosis, and progressive goitre; and it is seen that, whatever may have been the source of the ptosis, the goitre undoubtedly came in from an entirely distinct stock. Many analogous cases might be quoted.

Reference has been made to cases in which a heritable condition, though apparently limited to one anatomical or physiological system, may invade different parts of that system in different persons. The best of the well-defined cases is seen in the *trio*—retinitis pigmentosa, progressive nerve deafness, and feeble-mindedness or idiocy, diseases that seem capable of acting as mutual equivalents or substitutes; some correlation also seems to exist between Leber's disease and epilepsy; and of course the neuropathic constitution may show itself in several different forms of mental disease. Albinism is also complicated with defects of the nervous system in a disproportionate number of cases, and the association must therefore be looked upon as more than a coincidence. The possibility that early death may in certain cases represent a substitute form of a heritable disease has already been mentioned.

It appears that the individuals affected by hereditary imperfections and disease are very often members of unusually large sibships. This has been mentioned by Dr. James Taylor† in relation to hereditary ataxy, whilst Karl Pearson‡ concludes that both tuberculous and deaf-mute stocks are quite as fertile as, and probably more fertile

* Darwin makes a general statement to the same effect (*Animals and Plants under Domestication*, ii, p. 56).

† James Taylor, *T.O.S.*, xvii, 1897, p. 63.

‡ *A First Study of the Statistics of Pulmonary Tuberculosis*, 1907, p. 20.

than, normal stocks of the same social class. In regard to more general signs of inferiority we are told by Mr. Heron that, at any rate for the London districts, "there is a very close relationship between undesirable social status and a high birth-rate.* We shall see presently that the same is apparently true for retinitis pigmentosa and other eye diseases. Some caution, however, is needful in concluding that large birth-rate and disease are as closely connected as they appear to be; for some pedigrees of disease have been selected for investigation just because they contain large numbers of accessible members, and the prevalence in them of large childships may be only what is normal to the particular population, class or stock.

I will refer next to the question of sex liability in some of the hereditary eye-conditions.

We have first the sex-limited group—ordinary colour-blindness, Leber's disease of the optic nerves, and one form of congenital stationary night-blindness. In these so large a majority of the affected persons are males that affected females are regarded as rare exceptions; and this rule holds in general terms for each separate family as well as for the aggregate.

Next come diseases that have no special correlation with sex; the lump sum of males and females is about equal, or at most not widely different, although separate families often display marked departures from the rule, one having a great excess of males, another of females. The best examples are all forms of post-natal cataract, glaucoma (so far as we yet know), and a second form of congenital stationary night-blindness. Probably other diseases will be added to this group.

In the third group—containing all forms of congenital

* "On the Relation of Fertility in Man to Social Status and on the Changes in this Relation that have taken place during the last Fifty Years," David Heron, 1906, *Drapers' Company Research Memoirs: Studies in National Deterioration*, p. 21.

cataract, retinitis pigmentosa, albinism, and probably some of the less frequent affections, such as congenital day-blindness—we still find great discrepancies as to sex numbers in individual families, but when large numbers are taken a fairly uniform, though not extreme, preponderance of males.

As the sex-inequality in this last class cannot be accounted for by any obvious cause it is probably the expression of some general law, and the following facts seem to support this view: (1) Although more boys than girls are born (about 104 boys to every 100 girls in England and Wales in 1907)* the inequality is more than redressed by the higher general death-rate for males so that the total living population shows a deficit of males (about 93 males to every 100 females in England and Wales in 1907). (2) The males die in excess chiefly (*a*) between birth and five years of age, (*b*) between fifteen and sixty-five; between five and fifteen the sexes die in nearly equal numbers (about fifty-one females to forty-nine males). The higher mortality of males under five, which alone concerns us now, is due chiefly to deaths from causes classed by the Registrar-General collectively as "immaturity," *i. e.* premature birth, congenital defects, teething and congenital hydrocephalus. In 1907 out of every hundred children dying from these causes under five years old fifty-six were males, forty-four females. (3) There appears to be a similar excess of boys over girls with various "defects of development," principally of the sense-organs and intelligence, such as Dr. Francis Warner described in 1894 in children at the elementary schools.† Dr. Warner's statistics show that if the number of boys and girls examined by him had been equal there would have been sixty defective boys to forty defective girls in every hundred of those selected by him as showing deficiencies.‡

* The data from which these and the succeeding statements are drawn may be found in the *Report of the Registrar-General.*

† Warner, Francis, *Report of British Association.*

‡ Since the above was written Mr. Alan Barlow has supplied me with

Archibald Garrod* states that the rare heritable conditions, alkaptonuria, cystinuria and pentosuria are all more frequent in males than females. In 157 subjects of these three diseases he finds no less than 113 males.

Now it is not a little remarkable, as regards the third group of eye diseases just mentioned, that in retinitis pigmentosa (1381 cases) and lamellar cataract (1793 cases), 62 per cent. of those affected are male and 38 female; whilst in other forms of congenital cataract (335 cases) and in albinism (upwards of 1000 cases) the proportions are not very different—about 55 per cent. males and 45 per cent. female. In day-blindness there is a considerable excess of males.

It is said also that there is a marked excess of males over females amongst deaf-mutes.

I feel sure that stores of information as to the relative liability of the sexes to hereditary disease must exist. But meanwhile the few facts now brought forward favour the view that, in man, the male is on the whole more liable than the female to many innate defects and diseases, and perhaps especially to such as affect the organs of sense and intelligence.

It is extremely important to know whether the inheritance of an imperfection influences the longevity of the affected who survive; either by the direct effect of the disease upon vitality as in diabetes or hæmophilia, or by

some figures from the Education Office, which, although probably needing correction in certain particulars, appear to point in the same direction. These figures are taken from the *Statistics of Public Education*, 1906–7–8, and refer to the number of children between the ages of five and sixteen attending schools for the defective and epileptic in England. The average number of children attending about 160 such schools in each of the three years mentioned was 10,464, of whom 6019 were boys and 4445 girls. The numbers are vitiated to some extent by the facts that (*a*) they include a certain number with physical rather than mental defects, and (*b*) boys tend to leave the schools at an earlier age than girls; but these two sources of error may not improbably tend to cancel each other, and in any case would not be likely to account for nearly all the difference between 57 and 43 per cent. shown by the above numbers.

* Archibald Garrod, *Inborn Errors of Metabolism*, 1909, p. 20.

its indirect power of lowering the resistance to hurtful influences. The purely hereditary diseases of the eye do not seem to have any relation to length of life, at any rate a good many old persons are found in pedigrees of cataract, glaucoma, retinitis pigmentosa, Leber's disease, and albinism. But the subject has not yet been at all adequately looked into; and attention may suitably be called to the importance of recording everything we can about age in every member of a morbid pedigree; age of parents at marriage; age at onset of the disease in those affected; age at death, especially when the disease has "anticipated."

Every effort should also always be made to get the order of all the births, or rather of all the conceptions, and the intervals between them. Only in that way can we find out whether a disease tends to affect the earlier or the later births to excess. Karl Pearson's studies of the statistics of phthisis, insanity and crime lead him to believe that the earlier born children are more frequently predisposed to those conditions than the later ones.* Laqueur considered that the first and second born were decidedly less likely to suffer from hereditary diseases of the eye than the third and later births; but his remarks were based on only forty-eight families, containing in all no more than 244 children.† Berry has pointed out that in a particular pedigree of cataract (Fig. 24) the eldest born girl of each sibship invariably had the disease.

Cataract.‡

(*Figs. 11 to 27.*)

It is well known that cataract often runs in families, sometimes appearing in several generations. This has been ascertained beyond doubt for several of the best-

* *A First Study of the Statistics of Pulmonary Tuberculosis*, 1907, p. 25, Boyle Lecture. Also *The Problem of Practical Eugenics*, 1909, p. 19, etc.

† Laqueur, *Zeitschrift f. Praktische Aerzte*, 1897, No. 21, p. 8.

‡ For the abbreviated titles of periodical publications referred to in this or subsequent sections see Appendix IX.

marked varieties, and will probably be found true for all as opportunities for investigation occur. When cataract occurs at birth, or early in life, in brothers and sisters, both parents being free and no history obtainable of ancestral or collateral cases, when it is, in fact, what is called *familial* without proof of heredity, there may be grounds for attributing it to some defect of intra-uterine nutrition. But this explanation, unlikely even when the mother is affected, is impossible when the father, not the mother, suffers, for in this case there must be a germinal cause. That the germ-cell, whether male or female, should be able to transmit a well-defined and often almost identical imperfection limited to so small a part of the body as the lens, and often to only a small portion even of it, shows how inconceivably minute the morbid germinal representation may be, and this whether we think of the lens itself or the parts upon which it depends for nourishment at different stages of its growth. From Priestley Smith's researches* we may take it that the weight of the normal human lens at between 20 and 30 years of age is about 175 mgrm. or roughly three millionths of the ordinary body-weight at that time of life.† Yet even this is too much. The opacity in a typical case of discoid (or "Coppock") cataract occupies only a small fraction of the entire lens, possibly one twentieth or even less. The malign germinal influence, whatever it is, presumably acts upon the lens only at its earliest stage, possibly even before the closure of the lens cup, and even then is so limited in its range as to damage no other part of the epiblast; or if another interpretation be preferred, affects no other part of the mesoblast than the minute portion concerned in the nutrition of the rudimentary lens.

In hereditary lamellar cataract the dimensions of the opacity are not so extremely minute, but it also, like the

* Priestley Smith, "On the Growth of the Crystalline Lens," *T.O.S.*, iii, 1883, p. 79.

† Average body-weight of ♂ + ♀ at 20 to 25 about 130 lb., or say 59 kilogrammes = 59,000,000 millegrammes ÷ 175 = 337,154, or, say, one third of a million.

discoid form, must be due to the influence of the male parent in many cases (*e. g.* Fig. 11). Some fairly large pedigrees have now been collected, and one of them seems to show conclusively that the discoid or "Coppock" form and ordinary lamellar cataract are essentially the same, and not, as we at first thought, independent forms; so that the two names, discoid and lamellar, should be used only when convenient for descriptive purposes. (In the pedigree furnishing Fig. 12 both forms occurred.) The discoid is probably only the smallest possible form of lamellar, so small that the two layers are united or indistinguishable. The position of the disc or flattened lamella at a deeper level than the nucleus of the normal lens, but in front of the posterior capsule, still awaits satisfactory explanation, though perhaps related to displacement of the nucleus backwards from some developmental cause.*

Opinions have differed for many years as to whether lamellar cataract of ordinary sizes is always congenital, *i. e.* actually formed before birth, or sometimes post-natal. I think the evidence is conclusive that it may be either one or the other according to the diameter of the opaque shell, but that in most of the *hereditary* cases the process occurs towards the end of fœtal life. The diameter of the human lens at the fourth month of fœtal life is about 3·3 mm., at the sixth month 4·5 mm., at the seventh month 5 mm., and at birth 5·75 mm.† Between birth and one year old the diameter is about 7·4 mm.‡ If shrinkage of the nucleus is the first stage in the formation of the opaque peri-nuclear layer the dimensions of the opacity may be a trifle less than the dimensions of the clear cortex from which the opacity was formed;

* According to Treacher Collins displacement of the nucleus backwards may occur in the fœtal lens as a consequence of faulty backward growth of the lateral lens-fibres. "Developmental Deformities of the Crystalline Lens," *The Ophthalmoscope*, 1908.

† Treacher Collins, *Researches into the Anatomy and Pathology of Eye*, 1896, p. 5.

‡ Dub, quoted by Parsons in his *Pathology of the Eye*, ii, 1905, p. 405.

thus if a lamellar opacity measures 6 mm. across, the lens must have had at least that diameter, or a little more, say 7 mm., before the opacity formed, and in such a case we should probably be right in concluding that the cataract developed shortly after birth.* Now the largest lamellar opacity that has been measured after extraction of the lens had a diameter of 6 mm.; the ordinary size is from 5 to 5·5 mm. In some it is much less, down to, say, 3·5 and 4 mm., and in these cases of small-sized opacity we should be justified in assuming that the morbid process had begun and ended before birth, even if there were no clinical evidence to that effect. There is, however, enough of such evidence to be convincing. We have first the observation attributed by Hulke† to Bowman about the year 1846, of lamellar cataract found in a kitten a few days old. Of later observations Hosch in 1897 published a case in which a mother had seen cataract in her baby's eyes at its birth, the diagnosis of lamellar being made by Professor Horner when the child was six weeks old and the opacity measuring 4 mm. across at the age of six years. The same woman detected the opacity in another of her children two days after birth.‡ Mr. Fisher has given me the case of a female baby (Fig. 14; IV, 2), in whom he diagnosed dense lamellar cataract at

* Collins, however, concludes that the opacity must always be antenatal if the part affected is, as is assumed, the most peripheral layer; or that if post-natal the part affected is not the most peripheral.

† Hulke (*T.O.S.*, vii, 1887, p. 27), defending in his Bowman Lecture (in 1886) the pre-natal formation of lamellar cataract, writes as follows: . . . "the first distinct recognition of lamellar and zonular cataract based on dissection was, so far as I know, made by Mr. Bowman, the subject being a kitten, killed and prepared for lecture in the physiological laboratory in King's College. The date of this was, so far as my recollection serves me, 1846, but it might have been slightly later." Mr. Hulke, who, as he tells us in another part of the same Address, was about this time one of Mr. Bowman's dressers, states that he (Hulke) wrote down at the time a description of the appearances although he was unable to find it at the date of the above occasion —1886. The kitten was only a few days old.

‡ Quoted as Case 69 in my paper upon "Heredity in Cataract," *R.L.O.H.*, xvi, p. 229.

three months of age, the history being perfectly clear that the opacity had been seen by the parents at fourteen days old, the child not having opened its eyes until then.

In another family of lamellar cataracts, one of the mothers (Fig. 11; Gen. III, 3), told me that she had seen the cataract within an hour or two of birth in more than one of her children, and as in some of them there was a conspicious white opacity at the anterior pole of the front layer, almost filling the pupil, I have no doubt she was correct in her observation.

After writing the above I had the opportunity of seeing the newly born male infant of a cataractous brother of the above woman (Fig. 11; Gen. IV, 14*a*), and found the usual small, perfectly well defined lamellar cataract, of about 4·5 mm., in both eyes exactly a week after birth (child born April 19th, eyes examined under mydriatic on the 26th); the cortex was clear so far as a moderately exhaustive examination in the mother's bedroom allowed one to see. Here also there was a dense anterior polar opacity which had been seen by the nurse and mother as soon as the baby's face was cleaned after birth.* In another case of typical small, dense, lamellar opacity (Dearsley) the clear testimony was that the opacity had been seen the day after birth. Lamellar cataract has doubtless been seen repeatedly at less than one year old.† Some of the small lamellar opacities have no doubt been described as congenital nuclear or perinuclear cataract.

The condition of the enamel of the permanent teeth in a patient with lamellar cataract helps us indirectly to decide the time at which the opacity was formed. It is

* Later still, on July 3rd, I examined IV, 19 in the same pedigree, a female born on June 19th, *i. e.* æt. 14 days, and found precisely similar, small, lamellar cataracts. On the same occasion I was told that IV, 15*a*, born in September, 1908 (after my original visit, which was in August), was certainly affected; it was a feeble baby and died in May; my informants were the mother, III, 10 and III, 11, who live in the same village, and may both be counted as skilled observers for this purpose.—E. N., July 11th, 1909.

† See *R.L.O.H.*, xvi, p. 228, Case 65, for such an example.

chiefly with the larger specimens of lamellar cataract that the well-known and characteristic deficiency of enamel in the permanent incisors and first molars is found, and Mr. Norman G. Bennett, after careful consideration of the evidence in connection with the date of formation of the enamel, has come to the conclusion that the cause of the deficiency is active from shortly after birth until about two years of age;* and that the correlated lenticular change is probably not ante-natal. He points out that the epiblastic elements of both lens and enamel become isolated within mesoblastic tissue, and that both might therefore not improbably be affected by a common cause of malnutrition.

Now I have myself often noticed that in cases of unusually small lamellar cataract (as well as in its minimal discoid variety), there is usually no defect of the enamel of the permanent teeth. This fact comes out strongly in all the extensive pedigrees of lamellar cataract hitherto published, for in these the opacity is almost invariably small and the teeth good.†

The conclusion, therefore, is that when lamellar cataract is hereditary the small size of the lenticular opacity, and the absence of dental deformity, both point to the cataractous change having occurred during intra-uterine life. It has been assumed that the visible results —lack of enamel for the permanent teeth and lamellar opacity in the lens—mark the *commencement* of the morbid process, but this can hardly be true, at least for the lens; something is probably wrong both in the lens and the uncalcified enamel before we can detect any

* Norman G Bennett, "Ætiology of Lamellar Cataract," *T.O.S.*, xxi, 1901, p. 42.

† Exceptions are, of course, seen, but I believe they are not very frequent or very well marked. See *R.L.O.H.*, xvi, p. 231, Case 74 and Case 75, 1 (Elizabeth). On the contrary, for confirmation of the general statement see Cases 72, 74 (mother), and 76, 5 (Louisa). The point is also illustrated in Fig. 12 (from *T.O.S*, xxviii, p. 226), where the only one (IV, 102) with large lamellar cataract had the characteristic teeth, whilst the teeth were normal in those with small-sized cataract.

change, and thus the number of cases that should be classed as intra-uterine is increased rather than diminished.

Fig. 11

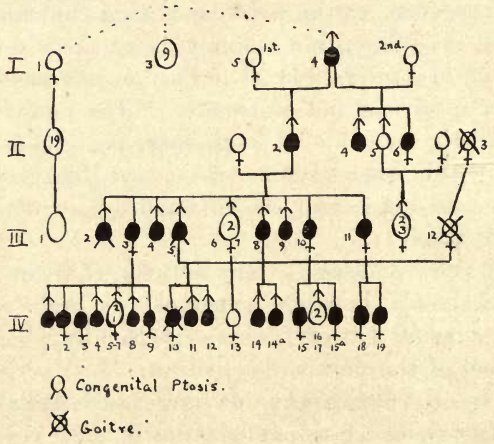
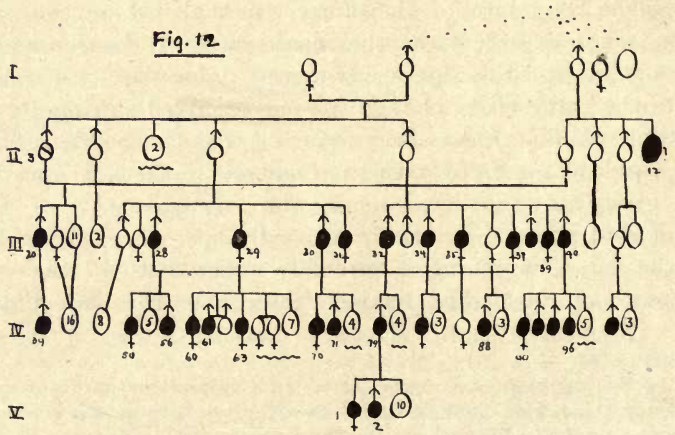


Fig. 12



The degree and manner in which small lamellar and discoid cataract may be heritable is shown in Figs. 11, 12, 13, 14, 15, and in sundry other pedigrees not exhibited

to-day.* Several new pedigrees are, I know, being worked out at the present time by members of this Society.

The descent of lamellar cataract appears to be always

Fig. 13

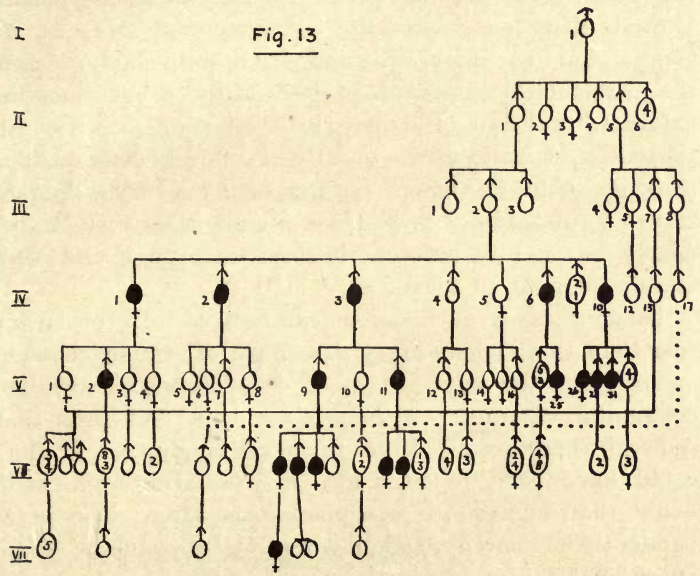


Fig. 14

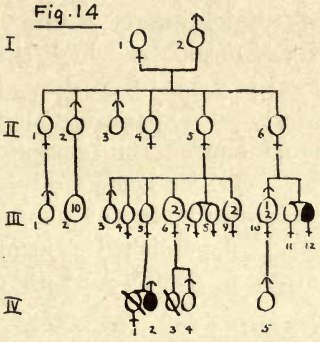
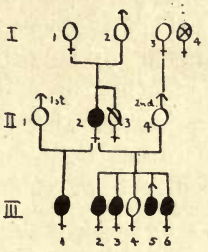


Fig 15



continuous, and there are hardly any consanguineous marriages. Lamellar cataract, whether hereditary or sporadic, is, I need hardly say, not confined to either sex ;

* *R.L.O.H.*, xvi, p. 225 *et seq.* and p. 395 *et seq.*

but whereas in senile and presenile cataract as a whole there are more females than males,* the reverse occurs in lamellar cataract. I have been able to collect, through the kindness of several friends in various parts of the United Kingdom, with the assistance of Mr. J. F. Cunningham at Moorfields, and from published sources, the particulars as to sex in 1887 subjects of lamellar cataract,† and find 1166 males to 721 females. Although the excess of males varies greatly in different batches it is present, little or much, in practically every separate return ; in a few lots the sex numbers are equal, or nearly so, and in only one is there an excess, and that merely nominal, of females.‡

Isolated cases of lamellar cataract, usually of larger size than in the hereditary cases, are of course common enough, and the same is true of other forms of so-called congenital cataract. Although we may feel sure that some of these would have furnished pedigrees if they could have been followed up, there is at present little doubt that such single specimens may often arise independently of hereditary influence, and be due to some nutritional defect confined to the individual.

I will refer next to the form of hereditary cataract that Mr. Gunn§ has named "coralliform," in which the principal opacities radiate forwards from the central part of the lens, ending anteriorly in expansions that appear to be tubular, and remind one of the separate "mouths" of a madrepore coral. Mr. Treacher Collins conjectures that these tube-like opacities lie in the planes of suture between the lens-fibres.|| I published a large pedigree of this form of cataract in 1905¶ ; another

* Nettleship, *R.L.O.H.*, xvi.

† See Appendix II.

‡ The numbers in the separate returns are given in Appendix II.

§ Gunn, *T.O.S.*, xv, p. 119.

|| Treacher Collins, "Developmental Deformities of the Crystalline Lens," *loc. cit.*

¶ Nettleship, *R.L.O.H.*, xiv, p. 218, Case 58 (Betts).

(Fig. 16), shown at a recent meeting here,* I owe to the kindness of Mr. Gunn and Mr. Leslie Paton; for a third, shown at the same meeting, I am indebted to Mr. Treacher Collins (Tomes family), and I know of others. The mode of descent is the same as in lamellar cataract. Although coralliform cataract is probably not very rare it has been apt to escape differential observation, its features not being prominent, whilst the characteristic trumpet-like or tube-like opacities are often intermingled with a number of discrete dots and spots of opacity. It is generally looked upon as congenital because it has been

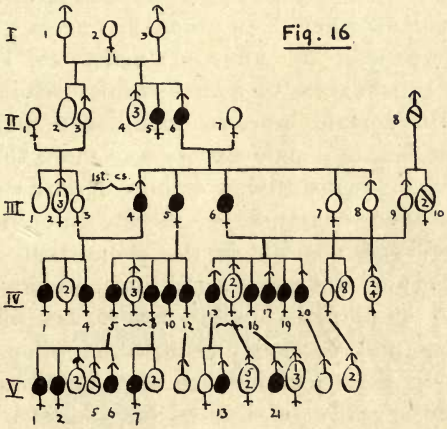


Fig. 16

seen several times in children, and only progresses with extreme tardiness; a middle-aged subject of the disease calls himself "short-sighted," and cannot remember ever seeing better; in old age nuclear haze is apt to increase the difficulty. We have, however, no record of coralliform cataract having been seen before the age of eighteen months.† Moreover, the average number and size of the

* *T.O.S.*, xxix (1909).

† In the Betts' pedigree (*R.L.O.H.*, xvi, p. 218, Case 58) Gen. IV, 23 was operated upon for the cataract at two years of age, his brother, IV, 22, at three years, and another brother, IV, 21 at about five. V, 12 was also operated upon at the age of five. IV 11, who died at eighteen months of age, was reported by other members of the family to have had cataract like the others.

characteristic opacities has seemed to me decidedly less in the young than in middle-aged and old subjects, and I am therefore inclined to think that in these people the lens may be clear at birth and for some months afterwards. But few of those affected have had anything done, and not much can be said about the outcome of operations; but there have certainly been several poor results. In the 68 known cases 36, or rather more than half, were females, 29 males, the pedigrees containing them showing a total of 167 persons—males 73, females 75, sex not recorded 19. These numbers are much too small for finality as to sex distribution; they may easily be upset by fuller data, as may be evident when I say that in one large pedigree (Betts) there were 20 affected males to 11 affected females—a great excess of males—whilst in the other five pedigrees the females were in such large majority that, in the whole six, the male excess was more than neutralised, leaving, as just stated, a definite majority of females.

We find similar examples of extreme difference between one pedigree and another in the proportion of affected males to females in many conditions besides cataract; precisely as in normal families where the offspring of some parents may be nearly all male, of others female.* No conclusion as to sex incidence of an hereditary disease, except it be a really sex-limited one, is worth anything unless based on very considerable numbers.

Of other distinct varieties hitherto included under the general title of "congenital cataract" accurate pedigrees will no doubt be forthcoming in future, and several incomplete ones might be quoted. In the best that I am acquainted with, given by Zirm and Bergmeister under the title "congenital stellate" cataract† (Fig. 17), at

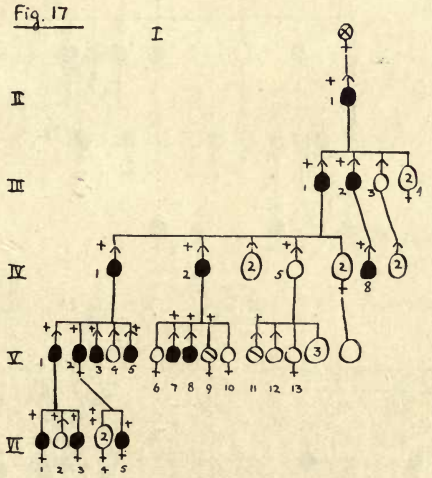
* *Cf. R.L.O.H.*, xvi, p. 188, for further facts as to sex-incidence in family cataract.

† Given in *R.L.O.H.*, p. 400, Fig. 54. The four younger generations appear to be completely recorded to date and contain fifteen cases of cataract in about forty persons; but the sixth generation, consisting of young children, may have increased since. Several other interesting pedigrees of cataract are to be found in the same paper.

least sixteen cases of cataract occurred in six generations, the disease as usual behaving like a "dominant."

It is much to be hoped that someone will collect information methodically about the minute vacuoles or dots of opacity so often seen in the lenses of the young; are they congenital, do they run in families, do they lead to cataract, and do they occasion, or only happen to accompany, the asthenopic symptoms from which their owners so often suffer?

Such minute changes have been noticed in several



members of congenital cataract pedigrees who were themselves free from the definite family complaint (*e. g.* in the families shown in Figs. 12 and 13). For the present it is uncertain whether such slight alterations are related to the family cataract or are merely accidental.

Post-natal or acquired cataract (Figs. 18 to 27), is often hereditary, and quite a number of pedigrees have been collected by many observers. A considerable number of these—I do not know what true proportion—show anticipation in generations and sometimes in successive siblings,

and the pedigrees I have chosen for illustrating the heredity of senile cataract to-day (Figs. 18 to 25), all illustrate this phenomenon in a greater or less degree.

Fig. 18

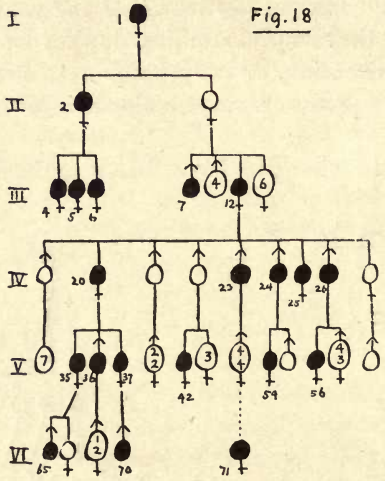


Fig. 21

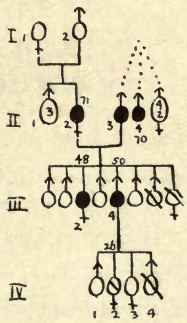
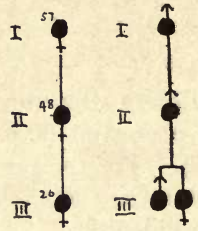
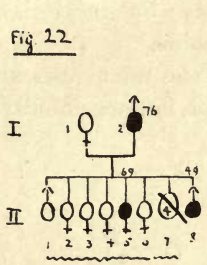


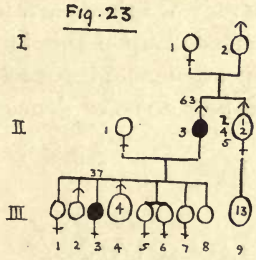
Fig 20 Fig 19

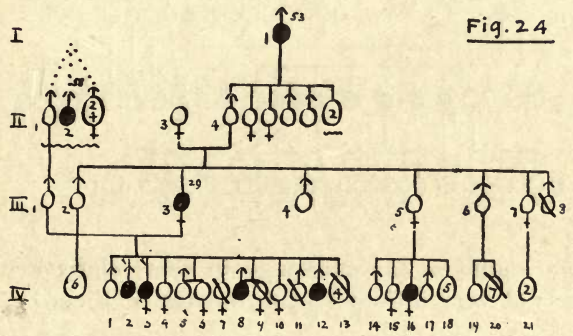


It is impossible to make the family record as full in hereditary senile cataract as in the congenital forms; the older members are scattered and may die with incipient cataract undetected. But we already know enough to say that senile, pre-senile and juvenile

cataract may be transmitted through several generations, that, as in the congenital forms, either sex may pass it on to either sex or to both sexes, and that the descent is, so far as we know, practically always continuous.* Although either sex may transmit, the tendency is, however, in fact, passed on oftener by women than men, and







not infrequently clings to the female sex through several generations of a long pedigree.

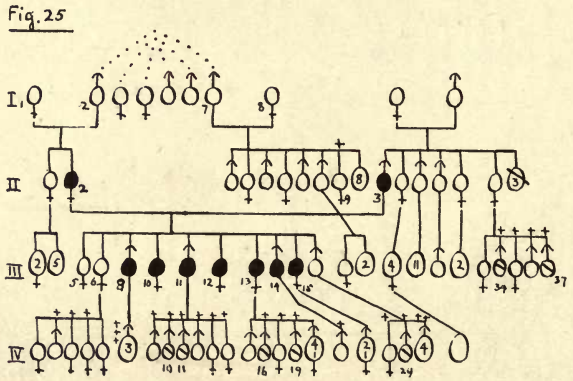
In one and the same family hereditary cataract often begins at about the same age in all who have it. But exceptions to this are very numerous, for, as we have just

* Apparent discontinuity, however, is seen in one or two places in a few pedigrees, *viz.*, in *R.L.O.H.*, xvi, p. 390 (Fig. 46); *ibid.*, p. 208, etc Cases 40, 80, 92, 100. The generation marked as normal in these pedigrees may, however, have contained some individuals with incipient cataract.

seen, hereditary cataract often occurs at an earlier age in the children than in the parents,* whilst in those of the same generation it frequently begins at about the same age in each. Fuchs† remarks that when senile cataract is a family disease it often comes on unusually early.

This earlier incidence in each generation—"anticipation"—is not known to be accompanied by disease or early degeneracy of other parts of the body; but more data are much needed upon this important point.

Of postponement—onset later in the next generation—there is next to no evidence in cataract, but ocasionally when



cataract begins at the same age in near relatives it may progress at very different rates in each of them.‡

* For good published pedigrees showing anticipation see *R.L.O.H.*, xvi, p. 179, *et seq.*, Cases 2, 4, 5, 7, 8, 15, 46 and 390; Dr. Green's Case Fig. 18 in present lecture, the numbers on which are from Dr. Green's figure and do not represent ages; *R.L.O.H., loc. cit.*, Cases 40, 41 (p. 208); a case published in *T.O.S.*, xxviii, p. 220 (present Fig. 25); another published in *T.O.S.*, xxix, p. 209 (present Fig. 24, giving some of the ages). Also Figs. 21 (Westly, Mr. Fisher's case) and 23 (Helyer, Dr. E. J. Smyth's case) now recorded for the first time, and giving the ages of onset. Figs. 19 (Sichel *fils*), 20 (Louis Stricker), and 22 (unpublished case of my own) all show the same feature and some of the ages are indicated.

† Fuchs, *Text-Book of Ophthalmology.*

‡ *R.L.O.H.*, xvi, p. 179, *et. seq.*, Case 13.

Cases are met with that may be called "hereditary infantile senile cataract," general opacity of the lens

Fig. 26

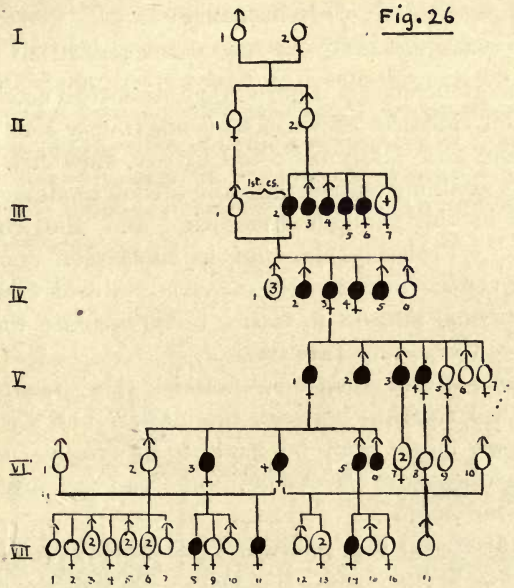
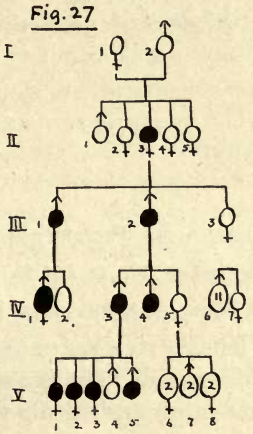


Fig. 27



coming on quite early in life (Figs. 26, Tatham Thompson, and 27, Berry). In the latter family the author states that

the opaque lenses were much harder than normal lenses of corresponding age.

Glaucoma.

(Figs. and descriptions 28 to 34 in Appendix III.)

About glaucoma as a hereditary disease I need not say very much, since the known cases (some twenty-four families) have been quite lately collected by Mr. Lawford. So far the most striking features are the strong tendency to anticipation in the younger generation and the continuous descent.* Probably many of us have seen one or two cases of typical primary glaucoma in children, and it will be of extreme interest in future to investigate the family history of these very rare cases.

In some of the glaucoma families there seems to be a possible relationship between this disease and myopia, and an attempt might well be made to ascertain whether, in such families, the two conditions can in any degree replace one another.

The prognosis for operation is another point whose importance needs only to be mentioned; in the members of some pedigrees the prospect is as good as possible, but I am inclined to suspect there are other families in which operation is generally unfavourable.

These and other considerations show how urgently we need the collection of much more material relating to the heredity of glaucoma.

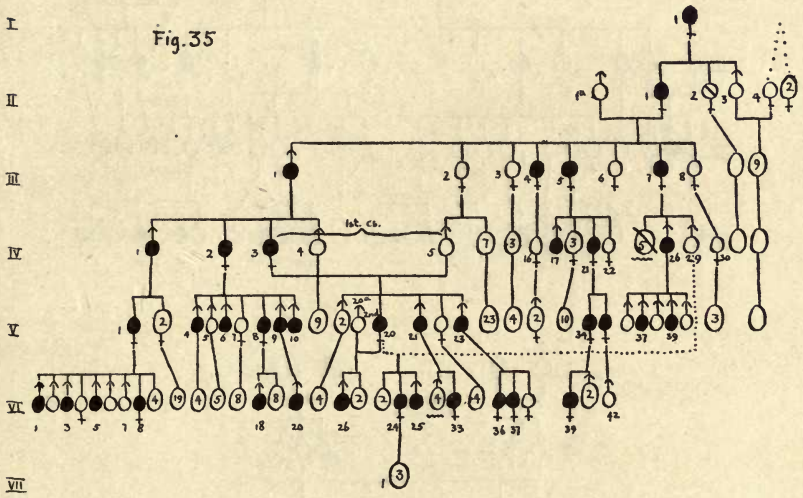
Retinitis Pigmentosa.

(Figs. 35 and 36 in text; 37, 38 and 39 in Appendix IV.)

This malady, which, especially since Liebreich's observations in 1861, has been a rich source of material to those interested in the influence of heredity and of consanguinity in family disease, has lately been dealt with at some length

* Lawford, *R.L.O.H.*, xvii, 1907, p. 57. Anticipation is shown in Cases 1, 3, 6, 7, 8, 10, 11, 13, 14, 15, 16, 17 and 24 of the series. Only one, Case 2, shows discontinuity of descent.

elsewhere,* and to-day I need only allude to some of the principal points and ask attention to some of the unsettled problems in the natural history of this disease and its equivalents. I will keep almost clear of numbers, but may mention that the paper referred to was based upon notes of nearly 1000 families (strictly 976) containing an average of close upon two ascertained cases of the disease in each. There was proof of heredity in one quarter of the families and of consanguinity of parents or ancestors of those affected in another quarter (I use round numbers, the



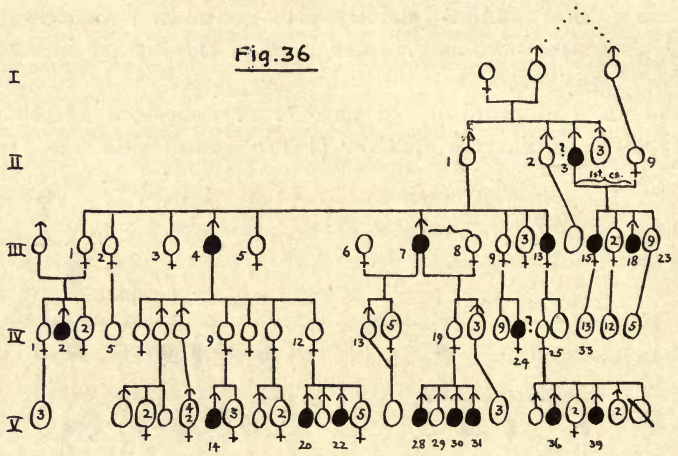
exact figures are given in the original paper). In the remaining half, where no history of either consanguinity or heredity was recorded, the notes were often very imperfect, and there can be no doubt that such a history would often have been forthcoming had more pains been taken.

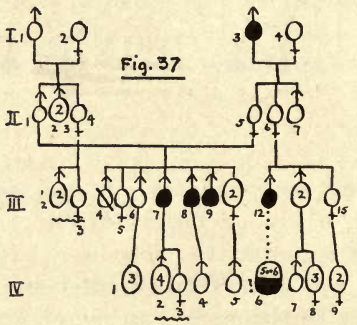
In the largest pedigrees† of retinitis pigmentosa the descent of the disease is continuous from parent to child, no healthy member ever producing affected offspring (Fig. 35).

* Nettleship, *R.L.O.H.*, xvii.

† To the fully recorded pedigrees quoted in the paper above referred to Snell has since added another in *T.O.S.*, xxvii, 1907, p. 217.

But we meet with some in which the direct line of transmission is without doubt interrupted by a healthy generation (Figs. 36 and 37).* I say "without doubt" advisedly, because the statement so often made by a





subject of this disease, that his or her parents had perfect sight and were not related by blood, though usually correct, does certainly need revision in some instances.

* Figs. 37, 38 and 39, not previously published, are fully described in Appendix IV.

A similar caution is necessary as to the families in which only a single example of the disease can be

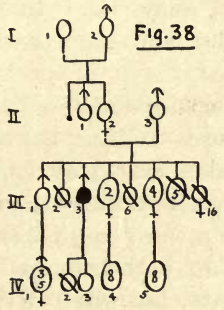
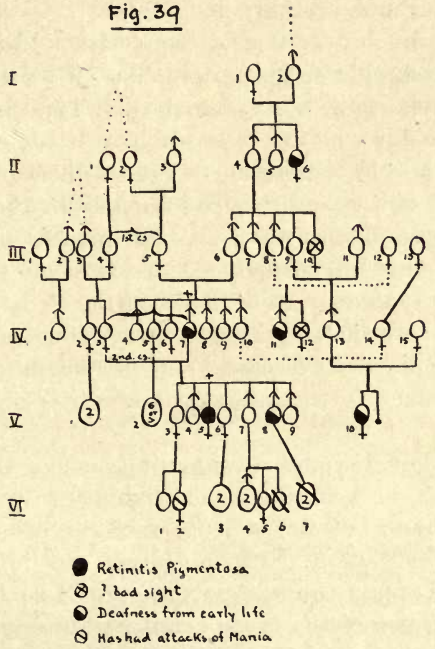


Fig. 39



discovered (Figs. 38 and 39); in some of these the disease may have existed latent in several members, but become

manifest only in the solitary one who was reached by some efficient determining cause. In others deafness or mental defect, easily omitted from the record unless directly sought for, may take the place of the eye disease (as in Fig. 39), and thus partly or wholly restore the continuity.

In respect to consanguinity we have to confess that but few of the records tell us the source and kind of cousinship, an omission that may very much lower their value. In future when taking the family histories of persons whose parents were cousins, it will usually be easy to record whether they both belonged to the affected side of the genealogy or not, and whether they were children of two sisters, or of two brothers, or of a brother and sister, or of a sister and brother.

Of the persons seen at all ages with retinitis pigmentosa a considerable majority are males (at least sixty males to rather less than forty females). This fact may, as suggested before, be an expression of some wider law; but two other interpretations suggest themselves for the time being, *viz.*, either that the females in these families die in excess before they are old enough to show the disease, or that the malady occurs most in the families that contain an excess of male births. It may be of interest to note that a marked excess of males is also seen in the chronic renal diseases, and in diabetes, whilst the reverse is found in the interstitial keratitis of congenital syphilis.

Next to heredity and consanguinity comes the influence of ill-health in bringing out a liability to retinitis pigmentosa where, but for such an exciting cause, it might have remained latent. Probably such an influence may sometimes explain the solitary cases. Of such determining causes some of the acute exanthemata seem to be the commonest, but probably tubercle and syphilis and in rare cases even severe loss of blood may have the same effect (Fig. 38). We may suppose that anything capable of damaging the arterioles might determine the onset of

retinitis pigmentosa in a choroid and retina predisposed to the disease. This part of the subject is well worth more attention.

Retinitis pigmentosa may set in very early in life or even before birth; and on the other hand there is reason to believe that its advent is sometimes delayed until quite an advanced age. The amount and distribution of the pigment varies a great deal, but the extreme periphery of the retina is usually free even in cases of long standing; when visible vessels are ensheathed in pigment such vessels are, in my experience, always veins, *i. e.* the pigment travels in the direction of the blood-current. Retinitis pigmentosa *sine pigmento* is nearly always merely retinitis pigmentosa at an early stage before the pigment has accumulated in the superficial retinal layers and become ophthalmoscopically visible; but in rare cases, although the retinal atrophy progresses, pigment does not travel inwards in any quantity, and then the term *sine pigmento* may be appropriate even at a later stage.* There does not seem to be any correlation between the quantity of pigment as judged by the ophthalmoscope and the colour of the patient's hair, irides and choroid. Retinitis pigmentosa does not hinder fertility; the subjects of the disease often have very many brothers and sisters, whilst if they themselves marry they frequently produce many children; whether the average fertility is above

* A case which may throw an important side-light on the seat and nature of the early changes in retinitis pigmentosa has lately been published by Bordley (*Johns Hopkins Hosp. Bull.*, September, 1908). In a negro pedigree night-blindness occurred during five generations, and progressed through gradual constriction of fields to total blindness; in the older members there were ophthalmoscopic signs of pronounced arterio-sclerosis, but even in them no other changes and no pigmentation. In the pedigree of forty-three individuals thirty-four are marked as night-blind. There are some improbabilities in the record, since it is stated that there is no record of any normal-sighted member having had children, and that all eight children of one night-blind parent were affected. The occurrence of night-blindness in relation to disease of the liver is the subject of an interesting section in Parsons's *Pathology of the Eye*, iv, p. 1292.

the normal can perhaps hardly yet be either asserted or denied. Until more, and more precise, data are collected, we cannot tell whether the order of the birth of the children, or the age of the parents at marriage, have any influence in determining the disease. The relative frequency with which the same fundamental cause produces retinitis pigmentosa in one, deafness in another, and mental inferiority in a third member of the same pedigree, has not yet been worked out; but we find on the other hand that certain stocks produce only retinitis pigmentosa and others only the equivalent deafness. It is especially noteworthy that the largest pedigrees of the retinitis are quite free from the other degeneracies, and the survival of such families is probably due to this circumstance.

I should like to return for a few moments to the two kinds of descent, continuous and discontinuous, met with in this disease. As I said in my introductory remarks, continuous descent in Mendelian terminology usually means "dominance," and interrupted descent, *except in sex-limited conditions*, means "recessiveness." Retinitis pigmentosa, although more frequent in the male, cannot be put into the sex-limited class with colour-blindness, Leber's disease and others in which women very seldom suffer. Therefore since, as Figs. 36 and 37 show, pedigrees exist in which a healthy generation always comes in the direct line between two that contain retinitis pigmentosa, or one of its equivalents, and since the normal "carrier" may be of either sex, the disease must then, in Mendel's terms, be recessive.* And yet in the largest pedigrees the descent, as I have already said, is always continuous and the disease therefore dominant.

This is as far as we can go at present. In the discontinuous pedigrees we can make sure that the intervening generation has neither eye disease, deafness nor mental defect; but there may perhaps be other morbid states, other equivalents of retinitis pigmentosa, that give no con-

* For the data see Appendix I *d*.

spicuous signs, and at present, therefore, escape detection. This is mere speculation for future work; the arteriole disease leading to retinitis pigmentosa, or to deafness or mental deficiency, may possibly in some cases affect an entirely different region, *e. g.* the arterioles of kidneys or liver or even of the hands or feet. But at present, if we are to test our data for retinitis pigmentosa by the Mendelian scheme, we must assume that change in mode of descent means change of dominance, however improbable this may appear. We were formerly content to say that a given disease or character could become latent for a generation or more and then re-appear, either capriciously, or perhaps when re-inforced by a marriage between cousins. But the Mendelian conception of pairs of complementary characters, one of which, in virtue of some attribute, dominates or prevents the appearance of the other, does not in its simple form allow the dominant to lose dominance or the recessive to gain it. But if the members of a pair representing a given character, say retinitis pigmentosa and its absence, could, without losing their affinity, become linked with, and influenced by, a pair representing some other character, a change of dominance in the original pair might conceivably be brought about, the second or linked character not necessarily attracting attention.* This is only the crudest possible indication of the ingenious hypothesis of "coupling," by which some of the complex and unexpected results obtained in experimental breeding are explained, and which appears to have been verified by control experiments in certain cases.

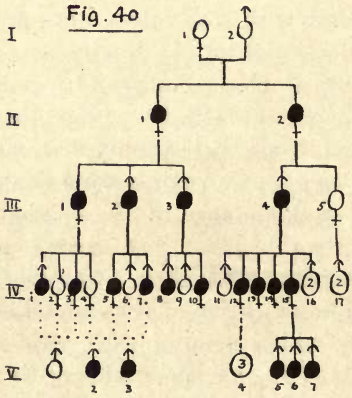
Of the varieties of retinitis pigmentosa, retinitis punctata albescens has, so far as I know, never been seen in a well-marked form in more than one generation, and if it is not a new departure, a "mutation," it must, in some cases, have skipped several generations.

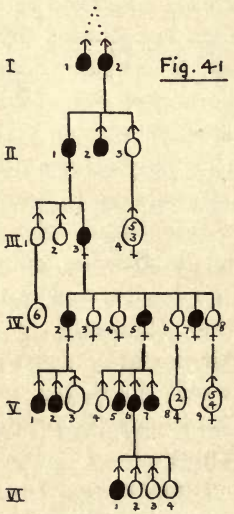
* *Cf.* Lock, R. H., "On the Inheritance of Certain Invisible Characters in Peas," *Proc. Roy. Soc.*, lxxix B., 1907, p. 28.

Hereditary Night-Blindness.

(*Figs. 40 to 43 in text; 44 in Appendix V.*)

Two sorts of hereditary night-blindness are met with which may be conveniently taken next, although they are, so far as we can tell, absolutely distinct from retinitis pigmentosa, and probably also from each other.* Both are, so far as can be ascertained, present from birth, stationary, and not associated with any other defects or degeneracies. In one of them the defect (it seems hardly





right to say disease) affects both sexes almost equally, descends continuously through either parent, and is not connected with any other peculiarity of the eyes or sight, nor with any unnatural appearances at the fundus. Besides the now well-known genealogy originally published by Cunier, there are only about half a dozen recorded pedigrees of this abnormality (Figs. 40 and 41 show two of them). Probably, however, the condition is less rare than

* A list of the cases, and the pedigrees of some of them given in Appendices I, G and H, and V.

we suppose, and now that attention has been drawn to it we may hope soon to hear of more cases. There has been no opportunity for anatomical examination, and nothing is known of the intimate nature of the night-blindness; we cannot even be sure whether its seat is retinal or cerebral.

In the other group of hereditary night-blindness shown in Figs. 42, 43, and 44 (Appendix V), the leading features are *limitation to males* with descent through normal-sighted females and *myopic refraction*, but visual acuity with cor-

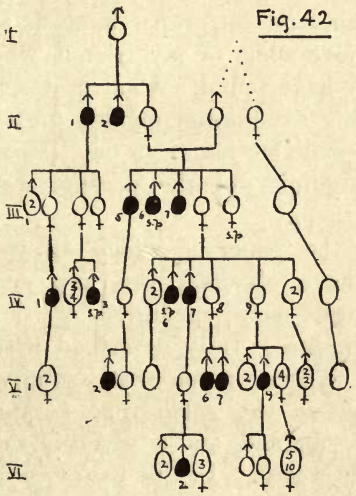


Fig. 42

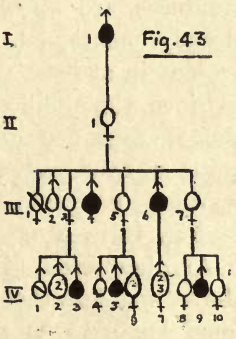


Fig. 43

rection often subnormal. Slight changes are sometimes found at the fundus, but even when present they are not constant either in character or situation. Considerable myopia has certainly been present in childhood in some of them, and perhaps in all; 3·5 D. to 9 D. are the usual figures, 11 D. the maximum recorded. No case has been found with steadily progressive myopia or severe myopic changes at the fundus. Colour-vision was normal in such as were tested. Nystagmus has been noticed in a few. Nothing is known of the nature of this condition; but the association of early myopia, frequently defective central

vision and occasional nystagmus, and the occurrence in some cases of various slight ophthalmoscopic changes, suggest that in this group the night-blindness, although congenital, is truly pathological, the result of a limited intra-uterine elongation of the eyeball interfering with the development of the choroid and outer layers of the retina. But why the condition should usually be limited to males is as great a mystery as in other sex-limited conditions. It is to be noted that ordinary myopes sometimes complain of seeing worse in twilight, but the significance of the symptom in such patients is open to more than one interpretation, and its proper analysis is full of difficulties, as I believe some of my friends who are investigating the subject have found. About a dozen fairly good pedigrees of this sex-limited myopic night-blindness are known, and may be found in my paper already mentioned. Consanguinity of the parents was present in at least three of them.

Since the publication of the paper in which all the above cases are given I have obtained the new and quite characteristic, although small, pedigree of this sex-limited myopic night-blindness, fully described with its Fig. 44 in Appendix V. There was no consanguinity.

Another case (44*a*), seen at the same time as the above, was less thoroughly examined, and is given in the same Appendix for what it is worth. In this case two of the three affected siblings were girls ; the parents were first cousins.

I owe these two new examples to the kindness of Mr. W. J. Cant and Mr. Clements, of Lincoln, who courteously allowed me and Mr. C. H. Usher to examine the affected members for ourselves last autumn. To the Rev. C. N. Usher, of Wellingore, I am indebted for the kindness and trouble he took in arranging for our meetings with the patients at his house.

Some few small pedigrees of night-blindness are found in which, though descent is discontinuous, the disease affects both sexes ; myopia appears to be common in the

affected members, but nothing like universal, and V. corrected is also apt to be subnormal. The relations of this group will have to be worked out by future observers.

Leber's Disease.

(*Figs. 45 to 52 in text, 48 being inserted at p. lxii.*)

The hereditary optic neuritis, or, as it is often called, optic atrophy, described by Leber, is so well known that I need dwell only upon certain points that call for further study.

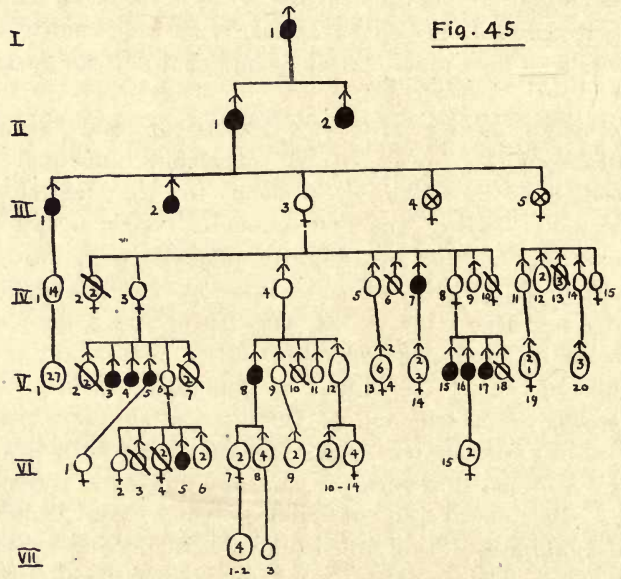
Although nearly always symmetrical and usually simultaneous in onset, it is sometimes unequal in intensity in the two eyes even to the degree of occasionally leaving one eye untouched, as in a case by Johnson Taylor,* or but slightly affected, as in Norris's case (Fig. 49, IV, 13), whilst an interval of weeks between one eye and the other is not very rare, and even years occasionally intervene (see Fig. 51). After an acute or subacute onset the climax is generally reached in a few weeks or months and no further change takes place, the leading permanent feature being a central or nearly central scotoma that varies in size and density in different cases. Peripheral loss of field is much less common. Total blindness is said to ensue in rare instances, but I believe this has generally rested on lay testimony. The usual age of onset is about 20 years. The subjects are males in a large majority of cases, but descent nearly always takes place through the unaffected mother. Consanguinity of parents is but seldom met with. In only a few cases do we find a history of other neuroses (most often epilepsy) in the patient or his relations. The following are good illustrative pedigrees of Leber's disease :†

* *T.O.S.*, xii, p. 146, Case 3. June 12th, 1909: Mr. Johnson Taylor has kindly re-examined the members of this genealogy quite recently and brought the history down to date. See Fig. 110, Appendix VI, *a*.

† For the other data on Leber's disease see Appendices I, 1, and VI.

1893. (Fig. 45.) Gould (George M.), *Pan-American Congress, Section Ophthalmology,* and *Annals of Ophthalmology and Otology,* ii, p. 303.

I, 1, blind rather late in life. II, 1 age at onset unknown, II, 2 at 40. III, 1 affected, died at 86; III, 2 affected at 28; III, 4 doubtful case, died at 40; III, 3 died at 62; III, 5 died at 74 and was blind in old age, cause unknown.



IV, 7 died at 40. V, 3 affected at 23, V, 4 at 28, V, 5 at 33, V, 8 at 52, V, 15 at 34, V, 16 at 28, V, 17 at 23, VI, 5 at 27. Author observes that the disease is dying out for want of child-bearing daughters in the later generations.

1893. (Fig. 46.) Gould. *Ibid.* Author's Cases 3 and 4.

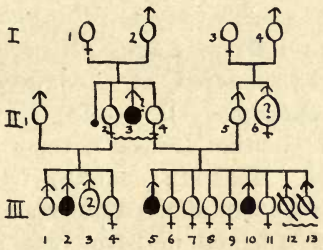
III, 2 affected at 25; his 4 siblings all living, 27 to 12. III, 5 affected at 24, seen at 36; III, 10 failed at 21, seen soon after. All very severe cases. Ages of III, 5 to 11, from 36 to 18; III, 12 and 13 died of "croup" at 3 and 2 years. II, 3 sight bad after smallpox at 40;

lived to 65. All in I and II lived to good age, and I, 3 was alive at 93.

1908. (Fig. 47). Hancock, *R.L.O.H.*, xvii, p. 167.

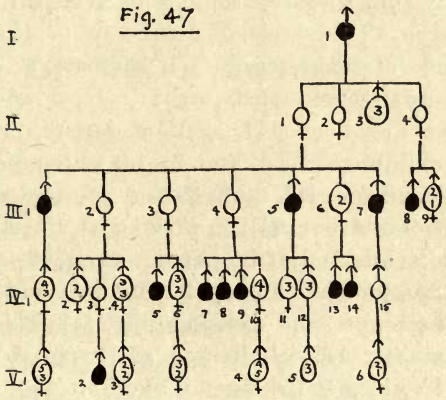
Twelve cases, all males, in 5 generations; 6 recovered

Fig 46



practically full V. in from twelve to eighteen months, *viz.*, I, 1; IV, 5, 8, 9, 13, 14; and III, 5 improved enough to resume business. III, 1, 7, 8; IV, 7 and V, 2 did not

Fig. 47



recover. IV, 9 very epileptic since 16; aged 26 at record. The following were intemperate in alcohol and tobacco: III, 1, III, 7; IV, 7, IV, 13, IV, 14. The following were very moderate in alcohol and tobacco, III, 5; IV, 5, IV, 8, IV, 9 (total abstainer from alcohol,

small smoker, epileptic, takes bromide). The age of onset was as follows: I, 1 about 25; 25 in III, 1, 5, 8, IV, 7 and 9; 26 in IV, 13; 30 in III, 8; 31 in IV, 14; 17 in V, 2; 41 in IV, 5. No early deaths. Descent strictly according to rule. Of the 12, 8 had no children and apparently did not marry; the 4 who married had at least 20 children between them. As to present age, IV, 14 is now (1909) 42; IV, 13, 41; IV, 9, 29. I, 1 died at a ripe age, about 100 years ago. No consanguinity.

1898. (Fig. 48, inserted at p. lxii, *supra*.) Klopfer, *Inaug. Dissert. Tubingen.*

The ♂ in VII (author's Case 5) reported to have had the same disease. In VIII (counting from the left), No. 1 (author's Case 4) was affected at or about 20. VIII, 4 (author's Case 2) affected in 24th year, seen soon after; three years later, no recovery; V. fingers. VIII, 5 (author's Case 1) affected at 21, seen six months later; five years later, no recovery. VIII, 6 (author's Case 3) affected in 20th year, seen three years later. Much consanguinuity, but disease probably derived through VI, 23.

1884. (Fig 49.) Norris, *T.A.O.S.*, iii, p. 662.

Four generations, 14 cases. I, 1 female, no details, but family records seemed trustworthy. II, 1 affected at 14, died 45; his first-born (III, 1), 45 at date of record, normal, had two children (IV, 1 and 2) of whose sight nothing known; second son, III, 2 affected at 18, died at 22. II, 2, normal, five children; III, 3 affected at 15, died childless at 50; III, 4 affected at 35, living, aged 50 at date; III, 5, 48 at date, and her husband, examined and found quite normal; they were not consanguineous; III, 7 normal, childless at 40; III, 8 affected at 19, aged 40 at date; two sons (IV, 14 and 15), aged 6 and 3 at date and normal. IV, 3, affected at 18, died at 30; IV, 4, affected at 14, died at 18; IV, 5, normal, 20; IV, 6, 18, no information to be got. IV, 7 to 13, issue of III, 5 and 6, all affected and all examined (author's Cases 1 to 7):—IV, 7 aged 22 at date (author's Case 5), failed at 14, stationary 3 years, then improved so that she could sew, and at date

V. $\frac{6}{24}$; IV, 8 (author's Case 6) affected at 19, no recovery in a year, V. $\frac{2}{60}$; IV, 9 (author's Case 7) affected at 18, under care at date; IV, 10 (author's Case 1), affected at 14, V. $\frac{2}{60}$, no recovery in nine months; IV, 13 (author's Case 4), affected at 7, seen at 8, V. of R. much worse than L., marked neuritic appearances in both, R. $\frac{6}{60}$, L. $\frac{6}{7}$; IV, 12 (author's Case 2), affected at $8\frac{1}{2}$, seen at 10, V. $\frac{6}{18}$, slight neuritic and atrophic changes; IV, 11 (author's Case 3) affected at 8, seen at 12 with V. $\frac{6}{18}$ to $\frac{6}{24}$ and O.Ds. pale.

1901. (Fig. 51.) Mathieu (Jules), *These de Paris*, No. 117, p. 51.

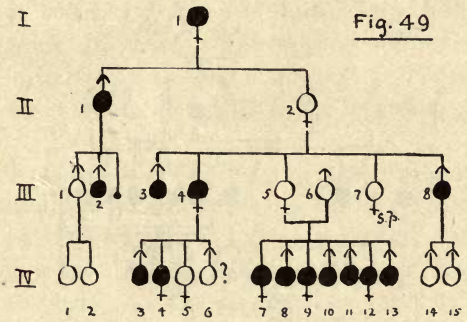
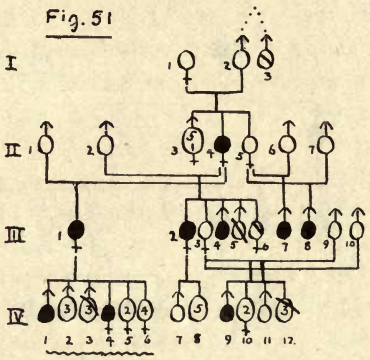


Fig. 49

II, 4 failed at 50, no recovery, lived to 69; her first child (III, 1) born several years before marriage, affected at 40 (author's Case 1). III, 2 born several years after III, 1, affected at about 40 (author's Case 3); III, 3 married twice; children by both husbands, but the two paternities not separated on pedigree; III, 4 affected at 22 (author's Case 2), living at record, not married; III, 5 died at two days; III, 6 died at 34, sight was "beginning to decrease." II, 5 had two illegitimate sons, III, 7 and 8 (who assert that they had different fathers), both affected at 28 and 32 respectively (author's Cases 4 and 5). IV, 1 to 6, 14 children of III, 1; IV, 1 (author's Case 6) affected between 16 and 19; IV, 4 (author's Case 7) attacked at same period of life, recovered completely; IV,

3 all died young, and IV, 6 all dead at record; IV, 9 (author's Case 8) affected about same age as IV, 1 and 4, seen at 25, improved very decidedly 2 to 3 years after onset. In III, 1 there was interval of 8 years between the two eyes, R. before L.; and in III, 8 between 2 and 3 years, R. before L. All the five affected ones in III had pterygium.

In respect to *prognosis*, the chance of recovery has, I think, been put too low—how much too low it is impossible to say. There do not seem to be any signs by which we can forecast the future for a given attack; but



with our present knowledge I am sure we not only may, but should, speak hopefully about any case seen within a couple of years from the onset or even longer. I find records of at least 25 affected persons (22 males, 3 females), in 16 genealogies who recovered either perfect or quite useful central vision; and minor degrees of improvement are probably rather common.* Most of these recoveries took place between the ages of 20 and 30, *viz.*, at the period when the disease is most frequent; but 2 were in children. In the same genealogy and even in the same sibship some may recover and others not: thus in Hancock's recent remarkable case (Fig. 47), 6 recovered out of 12 attacked; in

* Appendix VI, *b*.

one of Leber's earliest cases (1871), 3 siblings were attacked and all recovered; and in a case of my own 2 cousins recovered out of 4 attacked. In the recovered cases many different lines of treatment had been tried and we cannot be sure that any of them had much effect. A very important feature in these cases is the length of time that may elapse before noticeable improvement of sight begins, often 12 or 18 months, and, in one case, if we can believe the history, as much as 3 years. This possibility of considerable delay in recovery should lead to a more hopeful prognosis being given in future cases; one can, indeed, hardly doubt that the list of favourable results would have been longer had cases been more frequently followed up. Probably some of the "astonishing cures" of long-standing "blindness" of which we hear from time to time may have been examples of delayed recovery from this disease.

We shall probably be right in attributing certain cases that individually resemble the type but are without family history of the disease to the same essential cause, whatever that may be. Such cases, sometimes diagnosed as tobacco amblyopia, do not improve on ceasing to smoke and sometimes show contraction of fields as well as central defect. Interesting communications on such, possibly borderland, cases have been made by Lawford, and Edgar Brown.*

There is a tendency to anticipation in Leber's disease, both in successive generations and to a less marked degree in successive births in the same sibship; but the phenomenon is not so pronounced as it is in successive generations affected by glaucoma or by senile cataract.

Anticipation in successive generations was shown in 14 pedigrees out of 31 that gave the necessary information, the difference between ages of onset in the elder and younger generation being from 15 to 25 years. In 11

* *T.O.S.*, x, 1890, p. 166.

others the age of onset was practically the same in both generations. In only 3 cases was there evidence that the disease began later in the second generation than the first.* In the rare cases where a mother is affected the onset of the disease at an earlier age in her sons than in herself can hardly be called "anticipation," because the disease usually appears earlier in all males than in all females.

Anticipation in successively born brothers or sisters is not so frequent, being found in only 29 out of 82 completed sibships containing 2 or more cases of the disease. In 14 others the disease began at a later age in each successive birth, in 16 at practically the same age in each case, and in 23 the ages of the successive siblings when attacked varied irregularly. The differences of age-onset are of course much less between successive siblings than between successive generations, the age of onset in the junior sibling being usually about 3 years less than in the senior, and seldom as much as 5 years.†

It is of interest to inquire whether when a mother suffers from the disease her children will have it in greater numbers or with a different sex-distribution than if she had merely carried it as a potential in the usual manner?

In the corresponding case of congenital colour-blindness, Professor Bateson finds, as already mentioned, that if a woman be colour-blind the history always shows that her father was so, and that if she have sons they will *all* be colour-blind; whereas we know that in the ordinary case, where the mother is unaffected but carries the defect, only a proportion of her sons will have it.‡ Careful examination of the corresponding data for Leber's disease shows that it does not conform to this rule§ :—I. A man with Leber's disease who has children seldom transmits it;

* Norris, *Amer. Ophth. Soc.*, iii, p. 673, Cases 58, 75 and 93 in Appendix VI, *b*.

† For the data relating to anticipation see Appendix VI, *b*.

‡ Bateson, *Mendel's Principles of Heredity*, 1909.

§ The data for what follows are given in Appendix VI, *b*.

in 11 pedigrees 23 affected males became fathers and had 100 children who lived long enough to have the disease, the males and females being in about equal numbers; only 6 of the 100 became affected, 4 males and 2 females. II. An affected female has generally, like an affected male, had both parents normal; it is rare to find that she had an affected father or an affected mother. III. An affected female may transmit the disease to her children of either sex, but of her sons some usually escape. It is not clear why there should be this difference between colour-blindness and Leber's disease in the transmission to and by an affected female. We may note, however, that the one condition is an actually innate physiological defect, the other a disease of which in the vast majority of cases we cannot say more than that the *liability* to it is innate.

But although a woman suffering from Leber's disease does not, as a rule, give the disease to all her sons, she does give it to a larger proportion of her total issue than she would do if she only carried it incomplete or latent in the ordinary way:—I. In 12 completed sibships, where the mothers were affected but the fathers normal and the siblings of the necessary age normal, 64 children survived and 33 had the disease, *viz.*, 21 males and 12 females. II. In 38 similar sibships where the mothers were normal, but carried the disease (the fathers also being normal), there were 215 eligible children of whom 65 got the disease, 64 males and 1 female. In the first case one half, and in the second case rather less than one third of the children suffer, and the difference is almost entirely due to the excess of affected *daughters* in the first group, *viz.*, the group where the mother had the disease.

In one extraordinary case (Case 49, *supra*) all 7 children (4 male, 3 female) of the normal and unrelated parents (III, 5 and 6) had the disease, and had it unusually early in life.

The number of children born in the childships containing cases of Leber's disease is seldom less than the

normal, and is sometimes very large. In 44 completed childships, each containing one or more affected, with both parents normal, 28 contained 7 children or more, 10 of these having from 10 to 14 each, and one had 16. In 19 similar affected childships where one parent had the disease, 8 had 7 or more children, 2 of these having 10 and 2 having 14, 11 contained 6 or less. It is noticeable that in both these sets of sibships (44 and 19), those in which females as well as males were diseased averaged rather larger than those with only males diseased, as 8·25 to 7. The *normal* branches of affected stocks are seldom fully recorded, but in such of them as seem complete we find several containing 9 and 10 children each. So it is clear, on the whole, that the stocks in which Leber's disease is found are quite up to the normal in fertility, that the sibships in which the disease occurs are larger than normal, and frequently very large; and further, that the affected ones who marry often beget full families.

But if the births are too many the early mortality is large, sometimes very large, especially among the male children. This has been pointed out by several writers, notably by Gould. We find that in the sibships that have been reduced by a high early death-rate, the proportion of the survivors who get the disease is larger than in those sibships where few or none have died; almost half of the former became affected, including several females, but where no early deaths took place the proportion affected is one third.

One naturally suspects that a disproportionate number of those who died early would have suffered from the disease had they lived long enough, and that thus early deaths may contribute to the extinction of the disease; but this, of course, is at present a mere guess.

In several families there has been a high mortality from phthisis, but the number of such families is too small to justify any inference.

The characters of the disease are usually the same in

each individual at whatever age the attack occurs. In pedigrees where it comes on early, *i.e.*, before the fourteenth year, some females are usually affected; the reverse is true of the pedigrees where the onset is deferred until 30 or later, female cases being found in only a few of these. There seems, therefore, to be some connection between early age of onset and the female sex.

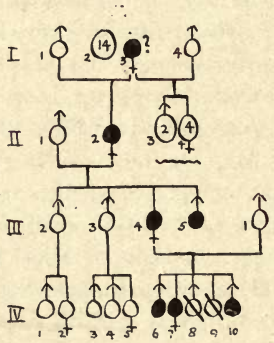
We have not much information about the longevity and causes of death of those who are afflicted, but the records show that a fair number were alive at 50 and later, up to 75; one died at 69, a pair of brothers at 72 and 73 respectively, and one man at 86. I have lately (thanks to the kindness of Mr. Doyne) seen a woman, now 71 (Fig. 52, II, 2), who has had the disease since birth or infancy; whilst in another woman, seen at 75 by Mr. Sym, the disease did not set in till she was 51. The subject is worth following up.

Case and Fig. 52, 1898 to 1909, unpublished, kindly communicated by Mr. Doyne, is a very important one.

I, 3 had some defect of sight, but not so bad as daughter (II, 2), and could do needlework and read; it may have been only myopia. Had 14 siblings (I, 2); her first child (II, 2) illegitimate, aged about 71 when seen (1909), sight failed in childhood, and has remained same ever since; symptoms and appearances characteristic in her and the other cases, all of which have been seen; has been very deaf for many years. I, 2 afterwards married I, 4, and had by him 2 sons and 4 daughters (II, 3 and 4), who all saw well. II, 2 married apparently after 30. Husband (II, 1) of about same age, afterwards lost both eyes from a boiler accident. They have had 4 children, who are all living; III, 2, aged 34 (1909), who has one living child, IV, 2, aged 8, normal, and one who died (IV, 1); III, 3, aged 32, normal, has 3 children (IV, 3, 4, 5), aged 5 years to 10 months, all normal; III, 4 seen by Mr. Doyne at 20 and by E. N. at 30 (1909), "born with the sight as it is now," is married to III, 1, who was examined and found normal; III, 5,

aged 29 (1909), single. IV, 6 to 10, issue of III, 1 and 4. IV, 6 believed to have seen well till about 3 years old, when he began to have to look about for things; when about 8 Mr. Doyne found myopia from 7 to 8 D. in each eye, with 3 D. of As. in R., V. fingers, O.Ds. pale; ordered – 7 D. In March, 1909, I (E. N.) found IV, 6 about the same; could read 3 or 4 J. slowly, held very close. IV, 7 saw well till about 4; at 5 Mr. Doyne found O.Ds. pale, V. fingers at 3 ft., refraction H. 2 D., no As.; in March, 1909, I (E. N.) found her in the same state. IV, 8 died at nine months with good sight;

Fig. 52



IV, 9, miscarriage. IV, 10 noticed by mother to see badly when two months old, or even earlier; at six months Mr. Doyne found irregular nystagmic movements, and noted that child did not follow a light; in March, 1909, æt. $1\frac{9}{12}$ years, I (E. N.) found the O.D. decidedly pale on Y.S. side, and the mother said the child saw so badly that he would run against the table or chair, and "has to look under the light to see." IV, 6–10 all suckled, intelligent, and show no other degeneracies; same general remarks apply to III, 4 and 5. Circumstances prevented proper examination of Fs. in any of these subjects, but it was quite evident from the manner in which they looked at objects that sight was best towards periphery; central

vision very bad in all, and they all have more or less nystagmus; O.Ds. much alike in all, pale all over in the adults, but especially so on Y.S. side; in the children nasal side is fairly coloured, but Y.S. side quite pale. None of those affected, from the grandmother (II, 2) to the youngest (IV, 10) are getting either worse or better. No consanguinity.

Apart from early deaths, we do not meet with any very prevalent morbid tendencies in these families. The most frequent seem to be epilepsy and aggravated hysteria; such conditions are recorded in several families, sometimes in the subject of the Leber's disease, sometimes in a sibling or a maternal relative. In one case Basedow's disease occurred in the sister of a man with Leber's disease.* Insanity or mental defect is recorded in three affected brothers, and in one other affected male, whose affected brother was epileptic. Diabetes is mentioned in two or three cases. At least two males, one affected, the other normal, and perhaps a third affected male, were congenitally colour-blind†—probably a normal coincidence; likewise, the association of retinitis pigmentosa with Leber's disease, observed by Wider, Coppez, and H. Schmidt, appears to have been purely accidental.

As to sex, I find about 60 females against about 300 males.‡ It has been said that in females the disease tends to come on with special frequency at about the climacteric, but little evidence of this can be found. Of the 57 affected females the disease came on before the age of 13 in 13 cases, almost equally spread over the

* Case mentioned (on Liebreich's authority) by A. Terson in his article "Maladies de l'Œil" in the *Traité de Chirurgie of Dentu-Delbet*, T.V., 1897, p. 198.

† Cases 106, 117, 147.

‡ The exact number depends upon the inclusion or exclusion of a few doubtful cases. There are probably more than 300 males to 60 females; small pedigrees with only males affected are relatively common and not always recorded, but cases in females have been more generally published on account of their rarity. Perhaps some few of the cases in females that I have included would be rejected as atypical by others.

25 years between 14 and 39 in 26 cases, in the critical years between 40 and 50 in only 10 cases.

We commonly notice that the age of onset is almost the same for all cases in the same genealogy—all very early in one, all unusually late in another. But marked exceptions are seen, as in a case (Fig 103) where one of two brothers lost his sight at 21, the other not until 60. The latter was diabetic at about the same period, and one cannot help suspecting that had he not been so he might have escaped the disease of his optic nerves.

Consanguinity of parents is seldom met with; I find at present only 6 or possibly 8 cases. In Arnold Knapp's case, given fully below, a woman with Leber's disease (Fig. 50; III, 3), whose father was also affected, married her normal first cousin, the son of a normal brother of the affected father. In Gunn's case* a woman with the optic nerve disease from childhood married her healthy first cousin and has so far two children, female and male, both affected at 3 or 4 years of age.

1904. (Fig. 50.) Knapp (Arnold), *A.* of *O.*, xxxiii, p. 383 (1904, and further information, March, 1909).

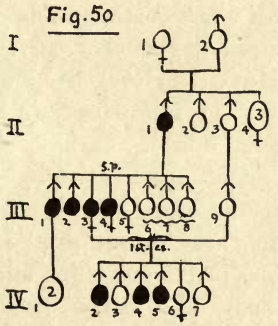
I, 1 and 2 normal. II, 1 failed at 24, recovered slowly enough to read, is now 67 (1904); had 2 brothers and 3 sisters, 1 of whom died at 17, 1 at 30, 1 at 67 and 2 still living; none affected. III, 1 to 4 all failed during their early school years. I, 1 has 2 sons, normal (1909). III, 2 lately married (1909). III, 4 married, no issue (1909). III, 3 married son of her father's brother; 6 children, of whom IV, 2, 4 and 5 all failed at early school age. IV, 3 and 6 remain normal, ages 15 and 9 in 1909. IV, 7 died at 4, with good sight.

This scarcity of consanguineous parentage in the history of Leber's disease is what we expect in a sex-limited affection. In such a disease, as already shown (Figs. 1 to 5), when two unaffected cousins marry only one, the wife, can possibly carry the disease, since the husband will so far as we know always show it at the proper age if he contains

* Fig. 46, Appendix VI, *a*.

it*; here, therefore, the cousinship does not increase the risk to the children. Next, if the cousinship comes through the wife's unaffected father she will not, any more than her unaffected husband, contain the disease, and might have been unrelated so far as risk of this particular disease is concerned. The only case in which a cousin marriage increases the risk is when the man is affected with the disease and his cousin wife carries it latent, deriving it either from her affected father or through her mother from an affected male of an earlier generation.

The differential diagnosis of Leber's disease, generally



easy, may now and then be difficult when we have to distinguish it from familial optic atrophy associated with tower-skull and other cranial deformities.† I have provisionally included the cases by Rampoldi and Suckling, which, although probably genuine, presented some unusual features and are not described in sufficient detail; and one of Higgens's cases is also included, although the author seems inclined to think that syphilis in the mother may have taken a share in causing the optic atrophy that

* But compare the suggestion on last page as to the possible influence of diabetes or other agencies in exciting a latent tendency to the disease.

† Patry, "Contribution à l'étude des Lésions Oculaires dans les Malformations Craniemes," *Thèse de Paris*, 1904. Several cases of tower-skull or oxycephaly will be found in the *T.O.S.* and elsewhere in British literature.

occurred in three of her children; (these three are Figs. 181*a*, 181*b* and 181*c*, Appendix VI*a*).

Cases of family or hereditary *congenital* optic atrophy have been described as if forming a group in some way distinct from Leber's disease. I believe that most of these are true Leber's disease setting in very early in life or perhaps sometimes before birth. Certainly several of those given in Appendix VI*a* present the classical symptoms; and I doubt whether we have at present sufficient evidence to justify us in setting up any of these family infantile cases as a distinct group.

There does not seem to be any connection between juvenile Leber's disease and the cases of progressive failure of sight with slight macular and papillary changes, and coincident mental degeneracy, in children, described by F. E. Batten, Mayou, Sydney Stephenson and others.*

As outlying cases the following may be mentioned:

I have once seen double chronic stationary central amblyopia with partial optic atrophy coming on in an old man at about the age of 76, and ordinary acute retrobulbar neuritis, first in one eye, and after a year's interval in the other, in his daughter aged 23–24 who had symptoms suspiciously like early disseminated sclerosis (P. 49, 62 and 52, 146).

I also saw in 1881–1882 retrobulbar neuritis limited to one eye and following an attack of diplopia due to paresis of one of the rotators, in a man æt. 50 years,† whose daughter was under Mr. Holmes Spicer's care 20 years later, æt. 33 years, for retrobulbar neuritis of left eye, which relapsed slightly 4 years later (1906), when she also had threatenings of disseminated sclerosis.

Acute retrobulbar neuritis has also been seen in two sisters in more than one instance.

* *T.O.S.*, xxiii, 1903, p. 386, and xxiv, 1904, p. 142, *et seq.*

† *Ibid.*, iv, p. 210, Case 17.

Hereditary Nystagmus (Sections *a* and *b*).

Without attempting a thorough search, I have found about twenty-five pedigrees in literature under the title of "Hereditary or Family Congenital Nystagmus," and have added a few of my own. Generally speaking, more attention has been paid to the oscillation than to its causes, so that we are often unable to classify the cases in any natural order. One is almost reminded of the time when every case of obscure blindness was called "amaurosis."

It may safely be asserted that infantile nystagmus, as a family affection, is in the vast majority of cases a symptom of defective sight, and not due to a primary central cause. Our business is to find out the nature of the amblyopia, and to arrange the cases accordingly. The defect of sight is always dated either from birth or early infancy; it is often due to some affection that causes little or no ophthalmoscopic change; and as the oscillation, especially in a baby or young child, often renders a refined ophthalmoscopic examination impossible, we may be unable to make an exact diagnosis until the patient is old enough to answer questions and have his visual functions tested. In some cases, however, we can come to a conclusion before that period.

Perhaps the first thing to note is that nystagmus in general is more easily produced in some persons than others; this is evident enough in cases where it follows blindness; and I am told that coal-miners and others do not all acquire it with equal facility under like conditions of work.* The same surely must be true for nystagmus produced in early infancy by defective sight; some infants will learn steady fixation sooner, more readily and with less perfect vision than others; those who have most

* The last letter I received from Mr. Simeon Snell, written a few weeks before his death, was in reply to a question I had asked him on this subject; it was to the effect that some coal-miners are more susceptible than others.

difficulty are likely, other things being equal, to develop nystagmus. Therefore, from time to time we meet with nystagmus dated from birth, or soon after, with only slight defect of visual acuity, such as may perhaps be due to nothing more than a moderate degree of astigmatism*; but as a rule the defect of acuity required to produce the oscillation is considerable.

Nystagmus dating from early life often becomes less marked in later years; it may even cease entirely, although such complete cure seems to be rare. Nystagmus is often less marked in some one position of the eyes, a position constant for the same person, but not the same for different persons; it also varies much in the rapidity and range, and also the direction, of the movements.

We can seldom be sure of the precise date at which the nystagmus begins in albinos and others with congenitally defective vision. In some albinos, however, the oscillation has certainly not been noticed until the child was many weeks or even some months old, and the movements are slower and perhaps less rhythmical at first than they become afterwards. Albinotic infants not infrequently keep their eyelids closed for weeks after birth, and this has sometimes led to the report that albinos were born blind; but when such infants have been seen it has been found that, with the eyelids held open, they evidently perceived the difference between light and shade, and that the pupils responded to light.

There must be several different intra-uterine, or very early infantile, diseases or defects of retina, choroid, or optic nerve that, running in families, cause hereditary nystagmus; but for the present the two that stand out as best known are albinism of various degrees and the affection called, for want of a better name, "total colour-

* I am not yet convinced that astigmatism alone can produce nystagmus, because the frequency of astigmatism in albinos suggests a correlation between deficient pigmentation and the corneal deformity, and in cases of nystagmus apparently due to astigmatism only we are not yet in a position to exclude a defect in the retinal epithelial pigment.

blindness" or "day-blindness." A large unclassed residue remains, but in all probability had attention been paid in these cases to the colour-sense and to the pigmentation of the eye some of them would have been placed in one or other of the two categories just named.

I have nine or ten pedigrees illustrating nystagmus in families affected by what I look upon as incomplete albinism limited to the eyes, ten of nystagmus with day-blindness or total colour-blindness, and fifteen of unclassed nystagmus.

(*a*) Albinism.

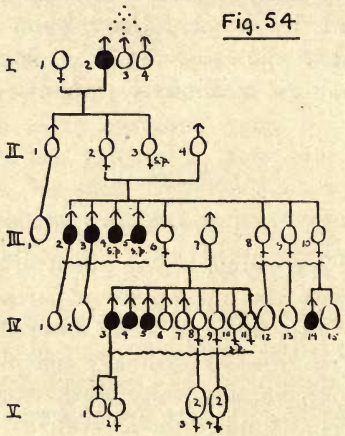
(*Figs. 54 and 55 in text; 53, and 56 to 60 in Appendix VII* a.)

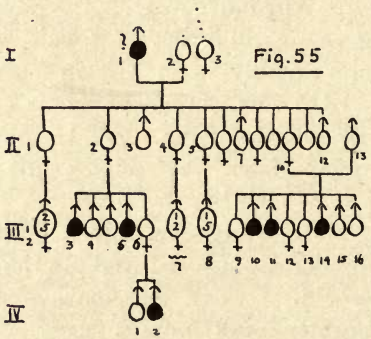
What little I have time to say about albinism must be in connection with the incomplete or partial cases that, as I believe, have often hitherto been entered as hereditary nystagmus. Pedigrees of ordinary conspicuous albinism with and without consanguinity, with continuous or discontinuous descent, and with, as well as without, other correlated or coincident disease, are seen in Figs. 56, 57,58, 59, 60 in Appendix VII.* A typical case of the slight degree of albinism in which the deficiency of pigment falls mainly upon the eye is seen in Fig. 53 (Appendix VII) (Mr. Jameson Evans's case). Here a child æt. 15 months (Gen. IV, 1), had nystagmus, slight pink reflex from the pupils, grey irides, and nearly white hair; whilst its brother, when seen at six weeks old, had steady eyes, black pupils, grey-blue irides and yellow hair, "not so light as the elder one at fifteen months old." The one marked III, 9, æt. 8 years, with slightly pink pupils, grey irides, decided lack of pigment in choroid, nystagmus, from 2 to 3 D. of astigmatism and V., corrected, $\frac{6}{24}$, had hair of a light shade of dull-brown which had formerly been lighter. The prevalent hair-colour in the others was dull brown and the irides grey. In this family with nystagmus, had

* From a forthcoming memoir upon albinism by Professor Karl Pearson, Mr. Usher, and the writer.

the evidences of albinism afforded by the eyes of the two children above described (IV, 1 and III, 9) not been forthcoming, the true bearings of the case could hardly have been discovered.

In a case of my own (*Albinism Memoir*, Fig. 402)*, a





similar state of affairs existed, except that there was no nystagmus and V., with the moderate myopia and slight astigmatism corrected, was $\frac{6}{9}$. I have myself no doubt that Lloyd Owen's well-known case, Fig. 54 (*Albinism Memoir*, Fig. 449), was really albinism limited to the eyes

* This lecture, Fig. 186, Appendix VII.

and incomplete even in them. I put the same interpretation on Fig. 55 (*Albinism Memoir*, Fig. 410, my own case, Mansfield), and Figs. 187 and 188, Appendix VII.*

The note of all these cases is the blue or grey iris, hair now brown, but with the history that it was very fair or even "white" in early childhood, and a more or less albinotic fundus; almost all have nystagmus and marked amblyopia; when, as in a few of the cases, sight is good and the eyes steady, we must suppose that the retinal epithelium, at least at the yellow-spot region, is sufficiently pigmented, however lacking in pigment the choroid may be.†

* The suggestion that the cases just mentioned, and others like them were of albinotic nature was made, so far as I am aware, for the first time by myself in *R.L.O.H.*, xv, p. 110, 1902. It is evident that the idea of albinism was present to the minds both of Mr. Lloyd Owen in connection with Fig. 54 in 1882 and myself in relation to Fig. 55 in 1887, but it was mentioned by each of us at those dates, only to be dismissed.

† The hypothesis is that the imperfect sight, and with it the nystagmus, is caused by deficiency of pigment in the retinal epithelium; that this want may vary in degree, and may even, perhaps, affect only a part—say the central region—of the fundus; and lastly, that such relative or absolute lack of pigment in the epithelium is not recognisable with any certainty by ophthalmoscopic examination, the different depths of tint at the fundus depending far more upon differences of pigmentation of the choroid than of the hexagonal epithelium. In support of this speculation we may say (1) that in albinism with quite translucent iris, *i. e.* no pigment in the retinal layer, stroma pigment is occasionally present in sufficient quantity to give the iris an ordinary brown colour; (2) that microscopical examination of the choroid of normal European eyes shows—in the comparatively small number of specimens where attention has been carefully directed to the point—that the quantity of pigment in the retinal epithelium appears to be sensibly the same in eyes with pigmented iris and choroid as in those with iris and choroid almost, or quite, devoid of stroma pigment. Whether this position will be maintained when a larger number have been examined remains to be seen. Also we must be careful, for the present at least, to allow for probable differences in the *kind* of pigment in the eyes of European and of dark races; the eye-pigment of a Negro may be darker than that of a Scandinavian although the quantity be the same in the two. These are nice, but important, problems for future determination, and I have reason to believe that work is already in progress upon them. Examination of partly albinotic eyes, the so-called "wall eyes" or piebald eyes they might be called, of dogs and horses by Mr. Coats and Mr.

There are all sorts and degrees of albinism between these cases which I have ventured to include and the well-marked general albino whom we all know. It may be hoped that in describing future cases of hereditary nystagmus attention will be bestowed upon the present and past colour of hair, eyebrows, eyelashes and iris, aspect of fundus, colour-vision and refraction.*

In their heredity these partial cases appear to be almost perfectly sex-limited; of forty-three affected persons, forty were males, and the descent was through the mother in every case; no affected male ever had an affected child.† In these characters, the group I am calling incomplete ocular albinism differs from general albinism. It is true that in general albinism the descent is usually discontinuous, but the normal parent who acts as carrier is by no means always the mother; again, although there is a decided excess of males with general albinism over females it is much less than in the small

Usher within the last year have shown that—apart from the tapetum in those animals—every possible combination of pigment deficiency in the retinal epithelium and choroid or iris may be present, a result supporting, so far as it goes, the above contention. I believe we do not know anything positive about increase of pigment in the hexagonal epithelium after birth; but even if such increase were proved to occur in cases of incomplete albinism, it does not follow that visual acuity would be improved; the pigment might come too late for the otherwise developed retina to benefit by it; we know as a fact that improvement of visual acuteness in albinos, although by no means unknown, is decidedly rare. A great puzzle is the frequency and high grade of the ametropia and especially of astigmatism in nearly all recognised albinos, and the same problem meets us for these cases of blue-eyed nystagmus, and appears to furnish another link between the two groups.

* I do not suggest that everyone with blue eyes, nystagmus, and amblyopia is albinotic in any degree; but some certainly are so, and many others probably; whilst if the essential feature of an albinotic eye is lack of pigment in the hexagonal retinal epithelium, we are not yet in a position to deny the possibly albinotic nature of any clinical case where no more reasonable explanation of the nystagmus and defective acuity can be found.

† These small numbers are given for what they are worth. But even if a few other pedigrees of nystagmus are included where the evidence for albinism is even less than in the above, the excess of males affected over females affected remains very large – 3 or 4 to 1.

series mentioned above, being about fifty-five males to forty-five females.*

In the small series available (ten families) consanguinity has not been recorded in any, but I am not sure that inquiry was always made, and even if it had been we could not attach importance to the absence of consanguinity in so small a number. In general albinism consanguinity of parents is common. This fact together with the very great frequency of discontinuous descent in human albinism point to its being a Mendelian recessive. But apart from the question of correct numerical proportions, the infinite varieties both of degree and distribution of albinism in man, *i. e.* the frequency of intermediates, appears to militate against the applicability of the theory. This leads to the remark that in speaking of albinism we need a definition, and, without going into controversial matters with which, in the present case, I am not fitted to deal, I may at once say that, whatever may be true for such of the lower animals as have been fully examined, it is quite clear that for man we cannot limit the term to persons whose skin, hair and eye tissues are *perfectly* devoid of pigment. In the first, or last, place you cannot tell without microscopical examination whether a given skin or hair or eye contains a little pigment in certain places or none at all anywhere; and therefore if we refuse the term "albinism" when any trace of pigment is present we must refuse to diagnose albinism in man at all until someone has examined a human eye thoroughly and found it absolutely free from pigment. So far as I know this has not yet been done —not because such eyes do not exist, but because in themselves they are rare and the opportunity of getting them for anatomical examination enormously more so. Clinically we all know that every degree of defective pigmentation occurs in skin or hair or eyes, or in all together, to which we cannot refuse the term "albinism," qualified when

* In upwards of 1000 albinos of all races and various degrees, the excess of males is found not only in the aggregate, but in each separate group used in the summation.

necessary by such terms as "partial" or "incomplete." The problem for human medical observers is, not whether degrees of human albinism, either general or localised, exist, but how far we may carry our subdivisions—what are the smallest tracts or lowest degrees of deficient pigmentation that may be included in the species. It is, I think, likely, although we cannot as yet either prove or disprove the point, that *perfect* albinism of any one part does not occur without perfect albinism of the whole body. But as we have already seen for the eye, and as is well known also for the skin and hair, we find short of albinism perfect dissimilar degrees of it in the same individual, irregularities of distribution, and differences in the same tissue or organ at different periods of life.

(*b*) Day-Blindness with Total Colour-Blindness.

(*Figs. 61 to 64.*)

This interesting but rare hereditary disease is always accompanied by amblyopia, often of high degree, due to defect at the centre of the field; the fundus may appear normal, or slight changes about the macular region and at the disc may be present, not, however, such as would lead one to expect any serious defect of sight. There is always colour-blindness, and in the severer cases it is, as the title indicates, total, but in some milder cases the want of colour sense is less pronounced. No special kind or degree of ametropia is found. Nystagmus is a usual but not invariable symptom. The condition is always said to date "from birth," and it gets neither worse nor better with age. The patients almost always say they see best in a dull light, and sometimes put it that they are "blind" in bright daylight; this, the ordinary condition in toxic amblyopia, retrobulbar neuritis and central retinal disease, is often much more strongly marked in the condition I am describing. The disease often occurs in several siblings, but has, I believe, not yet been seen in parent and child; it is, however, known to have occurred

in two sibships of cousins and once or twice in an uncle. The total number of affected persons I have been able to find recorded, including the fifty-two collected by Grunert in 1903,* is eighty-four, including single cases without family history. Whether we consider this grand total, or only the instances of family prevalence, we find considerably more males than females with the disease with no corresponding excess of males amongst the healthy. There is, in the small series collected hitherto, a decided prevalence of consanguinity of parents. Mental defects have been relatively frequent either in the subjects of the disease or in collaterals. In these broad general characters the disease reminds us of retinitis pigmentosa—indeed, in one of my cases typical pigmentation of the retina was actually present,† and another case ‡ one was tempted to interpret as transitional between the two conditions; but the non-progressive character of the present affection appears to constitute an absolute difference.

No case has been examined post-mortem; Galezowski, who published one of the earliest of the modern cases (1868), conjectured that the seat of the disease lay in the cones, and Grunert, working on much larger clinical material and by improved methods, also sums up in favour of cone-blindness. It is interesting to note in this connection that Stock believes he has microscopical evidence that the bacillary layer is the first part to undergo visible change in retinitis pigmentosa.§

My first case (shown in Fig. 61), was so striking that as the disease seems still to be but little known, I venture to quote it from the paper in which it appeared almost thirty years ago.‖ This patient, an intelligent, fairly educated woman, æt. 25 years, came to St. Thomas's Hospital in 1879, with one of her sisters, who was affected like herself.

* Grunert, *A.f.O.*, 1903.

† Fig. 185, Appendix VII.

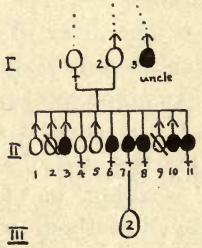
‡ Miss A—, *T. O. S.*, xxviii, p. 86, Case 9.

§ Stock, *Heidelberg Congress*, 1906 (published 1907) p. 48, and *Klin. Mon. f. A.*, xlvi, p. 226, 1908.

‖ *St. Thomas's Hosp. Repts.*, 1880.

The chief complaint was that she could not see by day and could not tell colours. She said that in the daytime her sight was so bad that she was afraid to cross the street though she could do it with ease in the evening, and that she could read small print by a light so dull that other people had to put away their books. She was so colour-blind that she always dressed in black and white to avoid making absurd mistakes. Her refraction was very slightly H., and V. $\frac{20}{200}$ and J. 6 held very close in daylight; constant slight lateral nystagmus. She saw worse after eserine had contracted the pupils. She sorted Holmgren's wools entirely according to their brightness, yellow looking the brightest. Disc and retinal vessels of healthy appear-

Fig. 61



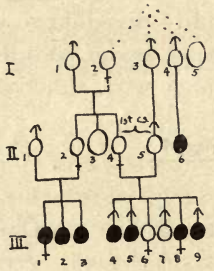
ance, but a slight whitish haze of doubtful meaning about the Y.S. A sister, æt. 20 years, who came with her had exactly the same defects of sight, and the spectrum to her was a band or stripe of one colour, brightest in the middle and darker at each end. I afterwards saw a brother, æt. 22 years, who was affected in the same way. They were members of a childship of 11, of whom 6 were living. The parents were said to have perfect sight and no colour defect, but an uncle was said to be colour-blind.

I afterwards saw a still more interesting family (Pike-Channon), (Fig. 62), in which two sets of cousins were affected, two of the victims being idiotic and quite blind. The colour-blindness of the brothers III, 4 and 5 was carefully examined by Captain, now Sir William Abney,

several years later and recorded in his work on colour-vision.*

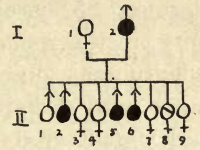
This case is given as two separate cases by Grunert, one attributed to me, the other to Abney. Fig. 63 shows another case carefully gone into by Mr. Holmes Spicer and myself several years ago, in which the father probably

Fig. 62



had the same disease. The last case I know of (Fig. 64), has been given to me recently by Mr. Holmes Spicer, with very careful and detailed notes taken by Dr. W. C. Souter in 1908. One girl and two boys, æt. from 8 to 6 years (IV, 4, 5, 6), are affected in a sibship of 8; only one other, a

Fig. 63

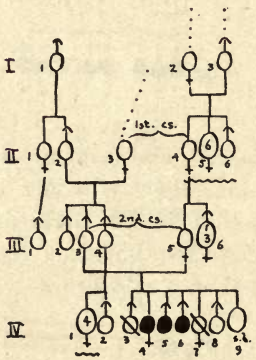


boy, æt. 3 years, has lived, and he appears normal; two died at 3 months, one at birth, and one was a miscarriage; no reason to suspect syphilis; parents second cousins through their mothers, who were first cousins. No other cases known in a fairly extensive pedigree. Family from Dorsetshire.

* Abney, *Colour Vision* ("The Tyndall Lectures," 1894), 1895, p. 126.

I have fourteen pedigrees of nystagmus not recorded fully enough to allow of their being assigned with certainty to either of the two classes we have just considered, or to any other recognised disease, although several of them are very extensive. Eleven of them are published, the latest being the one by Dr. W. H. Dudley.* Though these pedigrees are inconclusive as to the nature of the disease and probably in some cases not quite accurate in details, they are readily divisible to sub-groups, showing : (1) Continuous descent, seven pedigrees containing about 50 cases of nystagmus with defective sight, one of the

Fig. 64



pedigrees alone containing 25 cases; in two of these there was consanguinity, in the remaining five it was not mentioned. (2) Discontinuous descent; four pedigrees with more than 20 cases, only 4 being females; descent proved to be through unaffected mother in several instances; apparently no consanguinity in any. Mr. Ernest Clarke's case belongs to this little group, but is so extraordinary that I have counted it separately; this pedigree shows 22 males affected out of 23, and every one of the 20 females escaping; Mr. Clarke has been unable to see the recorder again in order to verify the particulars. (3) In three pedigrees the descent was

* Dudley, W. H., *A. of O.*, 1908.

continuous in some instances, discontinuous in others in the same genealogy; two of these (Audeoud, 1895, and Burton-Fanning, the same year), have evidently been drawn up with much care in all respects except as to the ocular details. A list of these pedigrees is given at the end of Appendix VII.

Choroid.

Data as to the family prevalence and heredity of various diseases of the choroid and of the cornea are beginning to accumulate.

(1) We know that central senile choroiditis is apt to occur in several brothers and sisters.*

(2) It is of course sometimes difficult to say whether a case should be classed *clinically* as choroidal or retinal. I have for convenience placed several family cases to which this doubt applies at the end of my recent paper on retinitis pigmentosa, *viz.*, one such group called atrophia gyrata choroidæ et retinæ by Fuchs, the other (rather paradoxically) a small series in which the choroid is congenitally absent except over a small area at the macular region.† Putting these two little groups together provisionally, we have 23 affected persons of whom 17 or perhaps 18 were male and 5 female. Five were, judging from the records, single cases; the other eighteen occurred in seven families, most of them in siblings only, but once in father and son and once in great-uncle and nephew. In one family the choroidal disease was associated with dulness of intellect, undergrowth of body, and arrest of sexual development. It is unnecessary to dwell longer on this group. The cases are evidently very rare, and in future examples the family history should be inquired into much more fully.

* Hutchinson *R.L.O.H.*, viii, p. 231, in three sisters (1875). I have recorded several such in *The Ophthalmoscope*, iv, 1906. Magers published one in 1889, *Ueber hereditäre Sehnervatrophie u. hereditäre Choroiditis Inaug. Dissert.*, Jena, 1899.

† The best known cases of these allied conditions are given in abstract in *R.L.O.H.*, xvi, pp. 369–377, 1908.

(3) In another group of cases a multitude of small, round, whitish dots or spots of what appears to be superficial disease of the choroid occupy the central area of the fundus, and in some examples pigmentary changes are described more peripherally. Mr. Doyne recorded the first definitely hereditary case of this variety in 1899,* using the term "honey-comb choroiditis." His patient was one of several siblings similarly affected, and the disease had occurred in the ascendants for three generations; I believe that Mr. Doyne has not hitherto published the genealogy of this remarkable family in full. A case probably of the same sort in a brother and sister had been published by Mr. Lang† in 1885, and a single case perhaps of the same type, without record of others in the patient's family, by Mr. Juler in 1893,‡ whilst in 1897 Mr. R. D. Batten and Mr. Holthouse§ recorded another single case, agreeing with the description of honey-comb choroiditis in a woman, aged 25 years, the last born of 24 children, 20 of whom had died young from some obscure cerebral disease. A case, probably similar, with coloured illustration, was published by Mr. Reginald E. Bickerton in 1900.‖ In 1901 Mr. Hugh Thompson¶ put on record the case of a woman, æt. 57 years, with extensive superficial choroidal changes around the discs which had caused no symptoms; but her father and three brothers who were his grandsons, *i. e.* were nephews of the patient, were night-blind, and one of them who was seen had the appearances of atypical retinitis pigmentosa.

The case given by Liebrecht** as retinitis punctata albescens in 1895 does not agree in all respects with that

* Doyne, *T.O.S.*, xix, 1899, p. 71.

† Lang, *T.O.S.*, v, 1885, pp. 140 and 141.

‡ Juler, *T.O.S.*, xiii, 1893, p. 143.

§ E. H. Holthouse and R. D. Batten, *T.O.S.*, xvii, 1897, p. 62, and xx, p. 95, with Plate III, fig. 2.

‖ Reginald E. Bickerton, *T.O.S.*, xx, p. 93, with Plate III, fig. 1.

¶ Hugh Thompson, *T.O.S.*, xxi, 1901, p. 66.

** Liebrecht, *Klin. Monats. f. Augen.*, 1895, p. 169. The case is quoted almost in full in my account of retinitis punctata albescens in *R.L.O.H.*, xvii, p. 392.

condition, and may, I think, have been of the same character as Doyne's "honey-comb" cases.

(4) In 1872, Mr. Cowell* published in much detail a peculiar case of destructive irido-choroiditis in a father and two of his children, and detachment of retina in a third child, but as the author thought that the whole affair was very probably syphilitic the case cannot be quoted with confidence as an example of heredity.

(5) I find notes of two sisters, æt. 20 and 21 years, seen at St. Thomas's Hospital in 1883, with identical extensive superficial choroidal atrophy which appeared to have come on at the age of 8 in one and 12 in the other, and was apparently not progressing; there was no pigmentation of retina and no evidence of hereditary syphilis. Both were myopic and had V. $\frac{20}{200}$ with correction. The cases may have been of the same kind as that of Miss A—, referred to in the Section on Day-blindness.

(6) I am indebted to Mr. Fisher for the notes of a case in which two sisters and a brother, æt. from 39 to 33 years in 1908, have changes similar to the last case (5) and dating, as in that case, from late childhood; the refraction hypermetropic. There was not the slightest facial or dental evidence of syphilis. They were the third, fourth and fifth born in a sibship of nine. The mother, who died at 53, had had poor sight for many years but was not blind.

(7) Two cases of family choroiditis have also been recorded by Hutchinson,† but in at least one of them there was a strong suspicion of syphilis in the father

Cornea.

(*Figs. 65 to 69 in Appendix VIII.*)

(1) *"Nodular" and "Reticular" Opacity of the Cornea.*

Of these conditions, classing them together as probably

* Cowell, *R.L.O.H.*, vii, 1872, p. 335.

† Hutchinson, *Archives of Surgery*, xi, 1900, p. 122; and *R.L.O H.*, v, 1866, p. 324.

of essentially similar nature, we have now at least eight pedigrees showing the disease in from two to four generations, quite half a dozen others of "familial" prevalence, and perhaps a dozen other single cases.

In the pedigree and familial cases the sexes are about equal, descent continuous with one exception, and from either sex to the same or to the opposite sex.

We shall no doubt have larger numbers to deal with before long.

Descriptions of the most extensive pedigrees (Holmes Spicer, Freund,* Doyne and Stephenson, and Folker) are given with Figs. 65 to 69 in Appendix VIII.

(2) Several other affections of the cornea are known to occur as family diseases from time to time.

In February, 1905, Mr. Jessop wrote to me that he had then lately seen conical cornea in a lady of about 50, who stated that her mother had gone blind from conical cornea. In June, 1906, I heard from Mr. Laws that he had just seen the case of a young woman with conical cornea, whose mother stated that the daughter's eyes had been like they now were from birth, and that three more of her children were affected in the same way; she had had eleven children, most of whom died in childhood; one was in an asylum; the parents were first cousins.

Buphthalmos has been seen in several brothers and sisters, and it is not unlikely that the case published by Crompton in 1840† as congenital opacity of the cornea in two siblings out of ten and the earlier one by Farar‡ in 1790, in three siblings, were of that nature.

* Freund's Case 2 (Bienert) has been brought up to date by the author in courteous reply to inquiry (June, 1909), and is now correctly shown by Fig. 67.

† S. Crompton, *London Medical Gazette*, xxvii, 1840, p. 432.

‡ Samuel Farar, "An Account of a Very Uncommon Blindness in the Eyes of Newly-born Children," *Medical Communications of Society for Promoting Medical Knowledge*, ii, 1790, p. 463.

APPENDICES.

The following appendices will enable the reader to verify the more important statements made in the Lecture, especially those as to the numbers of diseased to normal, the relative liability of the two sexes to be affected by each of the diseases in question, and the occurrence of anticipation. In some cases the data themselves are given, in others specific references are made to papers I have lately published which contain the necessary information.

The subject of Leber's disease is so important that I have thought it well to make a short abstract of every case published and unpublished that I could lay hands upon, and to insert figures of the pedigrees of a large number; this collection is based primarily upon Hormuth's *Dissertation*,* published in 1900, towards which the considerable series published by Habershon in our *Transactions* (vol. viii, 1888) furnished an important contingent. A number of other cases, published and unpublished, have been added to Hormuth's series.

The illustrative cases and figures are numbered serially from 1 to 188. Of these, 47 are inserted in the text of the Lecture, the remainder appear in the appendices in connection with their respective diseases. Although this plan will cause some inconvenience to the reader, it is preferable to the alternative of having two separate series of numbers, one for the Lecture, the other for the Appendices.

The following are the Appendices:

I. Illustrating the introductory section of the lecture.
   Frequency tables for:
   - (A) Cataract, post-natal.
   - (B) „ congenital, lamellar and discoid.
   - (C) „ „ other forms.
   - (D) Retinitis pigmentosa, continuous descent.
   - (E) „ „ discontinuous descent.
   - (F) Diseases allied to retinitis pigmentosa.
   - (G) Night-blindness, continuous descent.
   - (H) „ discontinuous descent.
   - (I) Leber's disease.
   - (J) Proportion of females carrying disease in certain sex-limited affections.

II. Relative numbers of males and females affected by lamellar cataract and other forms of congenital cataract.

III. Glaucoma, Case-figs. 28–34.

IV. Retinitis pigmentosa, Case-figs. 37, 38, 39.

V. Night-blindness without changes.
   - (*a*) References.
   - (*b*) Mr. W. J. Cants' new case of congenital night-blindness, Case and Fig. 44; also Case 44*a*.

* Hormuth (Philipp), "Beitr. z. Lehre v. d. hereditären Sehnervenleiden," *Inaug. Dissert.*, Heidelberg, 1900; published also in Deutschmann's *Beitr. z. Augenheilk.*, 89, Heft 42.

VI. Leber's disease.

(*a*) Abstracts of all the cases with figures, except Case-figs. 45–52 placed in the text of the lecture.

(*b*) References to cases or figures in *a*, illustrating various features of the disease discussed in the lecture.

VII. Nystagmus.

(*a*) Albinism section: (1) Case-figs. 53, 56, 57, 58, 59, 60.
(2) Various references to published cases and the following new cases, Figs. 182, 183, 184, and 188.

(*b*) Day-blindness section: Various references to cases and Case-fig. 185.

(*c*) Unclassed nystagmus; references to places of publication.

VIII. Cornea, Case-figs. 65–69. List of principal publications.

IX. Abbreviations for titles of periodical publications.

APPENDIX I.

Frequency Tables.

Data upon which the Statements at p. lxix et seq. of the Lecture as to the Relative Numbers of Normal and Diseased are based.

Only those sibships (childships) have been used that were either known or judged on good grounds to be complete as to numbers and sex record; only those in which (with one single exception) the youngest member was old enough to be susceptible to the disease in question; and only those in which either one or more of the siblings or one of the parents of the sibship was affected. Therefore, from the childships selected all members are excluded who died before the usually vulnerable age and all still-births and miscarriages. I am well aware that the omission of these items might lead to inferences that in the present state of our knowledge are unwarranted; for whether the numbers here given from human data do or do not agree with Mendelian requirements we are certainly not at present entitled either to affirm or deny that the proportions of normal and diseased would have been the same if all the conceptions had lived to the susceptible age. My object has been only to ascertain, on a somewhat larger scale than has been attempted before, how far the available numbers, as they stand, do or do not fit with Mendelian expectation as based upon experimental breeding.

In such diseases as post-natal cataract, very small lamellar or discoid cataract, and even retinitis pigmentosa, the proportion of affected to normal is almost certain to be more or less too low, for in these diseases, and especially post-natal in cataract, the earliest stages of the malady may pass undiscovered unless the eyes of every member be examined—a condition that can seldom be fulfilled.

When descent is continuous every completed sibship in which the disease occurs is counted, and every sibship of which either parent is affected, whether any of the children are so or not. When descent is discontinuous only the sibships showing the disease can be used.

(A) *Cataract: Post-nasal or Acquired Cataract, at all Ages.*

Reference.	Generation and sibship (childship).	Persons counted; affected and normal. ●+○	Number affected. ●
R.L.O.H., xvi, pp. 179–210 and 389–395.			
Case 1	III	6	2
Ibid. „ 5	II	8	2
„ „ 17	I	8	6
	II*a*	8	1
	b	5	1
	c	4	1
„ „ 18	II 10–2 *ob.* infancy	8	3
	III*a*	4	1
	b	7	1
„ „ 19	II*a*	4	2
	b	3	2
	III*a*	6	5
	IV*a*	3	2
	b	2	0
	c	6	0
„ „ 26	II	6	3
„ „ 27	III	9	5
	IV	8	4
	V	6	4
	VI*a*	5	4
	b	2	0
	c	1	0
	VII*a*	3	1
	b	1	1
	c	3	1
„ „ 28	II 8–1 too young	7	5
„ „ 30	II	4	2
„ „ 34	II	4	3
„ „ 36	II	5	1
	III	3	2
	IV*a*	3	2
	V*a*	5	4
„ „ 38	—	7	3
„ „ 46	II	13	9
	III*a*	5	3
	b	10	2
	c	5	3
	d	4	1
	e	4	1
„ „ 48	—	7	3
„ „ 98	III*a*	3	3
	b	12	2
	IV	9	5
	V*a*	3	3
	b	4	1
	c	2	1
	d	8	1
	e	8	0

Reference.	Generation and sibship (childship).	Persons counted; affected and normal. ●+○	Number affected. ●
Ibid. Case 100	II	6–1=5 (1 *ob.* inf'cy.)	3
„ „ 102	III	2	2
„ „ 105	I	6	3
	II	5	3
„ p. 408,	II	6	3
Casey Wood's	III*a*	8	4
Case 2 (Hussa)	*b*	5	2
	c	4	2
Ibid. Casey	II	6	3
Wood's Case 3	III*a*	7	2
(Smith)	*b*	4	1
T.O.S., xxviii, p.	II*a*	2	1
220	*b*	9–3=6 (3 *ob.* inf'cy.)	1
	III	10	7
Ibid., xxix, and	II*a*	4	1
Fig 21 in this	*b*	8	2
lecture (Westly,	III*b*	8–2=6 (2 *ob.* inf'cy.)	2
Fisher)			
Ibid., and Fig. 24	III	6	1
in this lecture	IV*a*	16–7=9 (7 *ob.* young)	4
(E. N., Oldfield)			
Ibid., (E. N.,	IV	8	4
Deasley)	V*a*	8	2
	b	7	1
Ibid., xxix, p.	III	8	2
(Fisher, Hiblen)			
Crzellitzer,	II	4	3
Deutsch. med.			
Wochenschr.,			
1908, p. 1894			
This lecture, Fig.	II	4	1
23 (E. N. and	III*a*	10	1
Smyth, Helyer)			
Ibid, Fig. 22	II	7	2
(E.N., St. John)			
Unpublished—	II	7	1
Mr. Hinnell's	III	7	1
case (Hall)			

Summary.

Total.	Normal.	Cataract.
126	—	52
135	—	60
132	—	54
47	—	11
440	263	177
(100)	(60)	(40)

(B) *Lamellar and Discoid Cataract.*

Reference.	Generation and sibship (childship).	Persons counted; affected and normal. ●+○	Number affected. ●
R.L.O.H., xvi, pp. 225–334 and 395–400.	III*a*	4	2
	b	6	1
	c	4	2
Case 62	*d*	4	2
Ibid. „ 66	IV*a*	3	2
	b	2	1
„ „ 69	II	5	1
	III	10	3
„ „ 70	II	4	2
„ „ 71		6	2
„ „ 72		7	2
„ „ 73		4	2
„ „ 77		8	6
„ „ 108	II*a*	7	3
	III*a*	9	0
	b	12 − 7 = 5 (7 *ob.* infancy)	5
„ „ 109	III	4	2
„ „ 110	V	6	3
„ „ 111	II	5	3
„ p. 215. Case 56	II	6	2
„ p. 408, Casey Wood's Case 1 (Charlton).	IV	12	10
This lecture, Fig. 11 (Everett)	II*a*	4	3
	III*a*	10	8
	IV*a*	9	6
	b	3	3
	d	3	1
Ibid., Fig. 12 (Stephens)	III*b*	6	4
	c	9	7
	IV*a*	7	2
	b	13	3
	c	6	2
	d	5	1
	e	4	1
	f	4	1
	g	9	4
Ibid., Fig. 12, *cont.* (Stephens)	*h*	4	1
	V*a*	12	2
Ibid., Fig. 13 (Coppock)	IV*a*	10	5
	V*a*	4	1
	b	3	2
	c	9	1
	d	7	3
	VI*a*	4	3
	b	6	2
	c	2	0
Ibid., Fig. 14 (Fisher's case, Pucknitt)	III*a*	5	1
Unpublished—Mr. Sym's case. This lecture, Fig. 15	III	6	5
Bishop Harman (Turner)	II	5	3
	III*a*	5	4
T.O.S., xxix, p. 101	*b* 8 − 2 = 6 (2 *ob.* young)	6	3
	c	2	0
	IV*a*	5	2
	b 2 − 1 = 1 (1 *ob.* young)	1	1
	c	3	2
	d	7	4

Summary.

Total.	Normal.	Cataract.
150	—	77
135	—	51
34	—	19
——	——	——
319	172	147
(100)	(54)	(46)

(C) *Congenital Cataract other than Lamellar: Coralliform, Stellate, and Undescribed Forms.*

Reference.	Generation and sibship (childship).	Persons counted; affected and normal. ●+○	Number affected. ●
R.L.O.H., xvi, pp. 211–216 and 400–408.			
Case 51		6	3
Ibid. „ 54	III	6	3
	IV*a*	7	1
„ „ 57		11	2
„ „ 57*a*	II	7	4
„ „ 58	II	8	6
	III*a*	5	3
	b	5	2
	IV*a*	2	1
	b	6	4
	c	10	7
	V*a*	3	2
	b	3	0
	c	5	1
	d	4	? 2 or 1
	e	2	1
„ „ 58*a*	II	7	2
„ „ 60	II	6	4
„ p. 233.	II	5	3
Case 78			
„ „ 112	III	5	2
	IV*a*	7	2
	b	1	1
	V*a*	5	4
	b	5	2
Ibid. Case 113	II	7	4
„ „ 118	II*a*	7	0
	b	5	2
„ „ 119	IV	6	3
„ „ 120	III*a*	7	3
	b	5	2
	IV	4	3
T.O.S., xxix, and this lecture, Fig. 16 (Perrin)	II*a*	5	2
	III*a*	5	2
	IV*a*	4	2
	b	8	4
	c	8	5
Ibid., Collins and E. N. (Tomes)	II	4	1
	III	7	3
Unpublished: Collins and E. N. (Revell)	II	13 − 3 = 10 (3 *ob.* infancy)	1

Summary.

	Normal.	Total.	Cataract.
	124	223	99
	(56)	(100)	(44)
Lamellar	172	319	147
	(54)	(100)	(46)
*Grand total.	296	542	246
	(55)	(100)	(45)

* *P.S.*—If we add two pedigrees showed at this Society by Mr. Bishop Harman at the July meeting (his Cases 1 and 2) the numbers are 306 (54 per cent.) normal, 206 (46 per cent.) cataract, total 566 (100).

(D) and (E) *Retinitis Pigmentosa.*

In compiling the following tables of retinitis pigmentosa I have omitted 9 childships—containing an aggregate of 70 children, the smallest having 6—each of which contains only one case of the disease, *viz.*, *R.L.O.H.* xvii, Cases 43, 81, 83*a*, 83*b*, 83*c*, 83*d*, 83*e*, 83*f*, 83*i*.

In the following 5 childships used in the tables either deafness or idiocy has been taken as equivalent to retinitis pigmentosa, *viz.*, *R.L.O.H.*, xvii, Cases 32, 2 r.p. + 1 idiot = 3; 33, 3 r.p. + 1 idiot = 4; 84, 3 r.p. + 1 deaf = 4; 119, 1 r.p. + 1 idiot = 2; this lecture Case-fig. 39, 1 r.p. + 1 deaf = 2.

(D) *Retinitis Pigmentosa—Continuous Descent.*

Reference.	Generation and sibship (childship).	Persons counted: affected and normal. ●+○	Number affected. ●
R.L.O.H., xvii, pp. 1–56, 151–166, 333–427. Case 1	III	8	4
	IV*a*	4	3
	b	1	0
	c	6	2
	V*a*	3	1
	b	7	5
	c	6	3
	d	2	2
	e	5	2
	VI*a* 12 − 3 = 9 (3 *ob.* infancy)	9	4
	VI*b*	4	0
	c	1	1
	d	7	3
	e	3	2
	f	3	1
	g	1	1
Ibid. „ 2	III	6	4
	IV*a*	11	5
	b	4	3
	c	1	1
	V*a*	3	1
	b	1	0
	c	12	8
	d	3	3
	e	4	2
„ „ 3	II	3	2
	IV	11 − 5 = 6 (5 *ob.* infancy)	2
	V	3	1
„ „ 4	IV	5	3
„ „ 6*a*	II	3	2
	III	7	4
	IV*a*	5	0
	b	6	2
„ „ 11	II	5	2
	III*a*	7	4
	b	5	0
„ „ 12	III	8	5
„ „ 13	II	6	2
	III	3	2
„ „ 28*a*	III	3	2
„ „ 29	III	4	1
„ „ 60	IV	7 − 1 = 6 (1 *ob.* infancy)	2
„ „ 44*a*	III	5	3
„ „ 76	III	12 − 2 = 10	4
„ „ 74	II*a*	6	2
	III*a*	4	2
Ibid. Case 62	VI	11 − 3 = 8 (3 *ob.* infancy)	5
„ „ 44	III	2	1
„ „ 53	III	12	4
„ „ 54	IV	5	3
„ „ 55	IV	7	5
„ „ 71	IV	3	2
„ „ 69	III	13 − 3 = 10 (3 *ob.* young)	5
„ „ 67	III	6 − 1 = 5 (1 *ob.* inf'cy)	2
„ „ 73	V	1	1
„ „ 68	V	9	3
„ „ 61	III	4	2
„ „ 65	V	4	2
„ „ 80*a*		10 − 2 = 8 (2 *ob.* young)	5
„ „ 84		9	4
„ „ 89	III	6 − 1 = 5 (1 *ob.* infancy)	2
„ „ 92		4	4
„ „ 104	II	5	3
	III*a*	1	1
	b	12	10
	IV*a*	2	1
	b	1	1
	c	9 − 4 = 5 (4 *ob.* infancy)	1
„ „ 118		8	3
„ „ 119		6	2
T.O.S., xxvii, p. 217 (Snell).	III*a*	3	1
	b	7	4
	IV*a*	4	0
	b	9	4
	c	3	0

Summary.

Total.	Normal.	Affected.
115	—	61
120	—	53
152	—	75
387	198	189
(100)	(51)	(49)

(E) *Retinitis Pigmentosa—Discontinuous Descent*, i. e. *Parents Normal; Both Sexes Affected.*

Reference.	Generation and sibship (childship).	Persons counted; affected and normal. ●+○	Number affected ●
R.L.O.H., xvii, p. 17, *et seq.* Case 15	IV*a*	11 – 4 = 7 (4 *ob.* young)	3
	b	1	1
Ibid. „ 15*a*	III	4	2
„ „ 15*b*	III	8	7
„ „ 16	III	5	3
„ „ 18	III	4	2
„ „ 20	III*a*	8	3
	b	13	6
„ „ 25	III	6	3
„ „ 26	III	7	4
„ „ 27	III	4	2
„ „ 32	V	5	3
„ „ 33	III*a*	9	4
„ „ 38	IV	4	1
„ „ 40	IV	4	1
Unpublished case: Mr. C. H. Usher (Rowand), lecture, Fig. 37	III*a*	8	3
	b	4	1
This lecture, Fig. 36 (and *T.O.S.*, xxviii, p. 226)	III*a*	11	4
	IV*a*	4	1
	V*a*	4	1
	b	8	2
	c	4	3
	d	7	2
R.L.O.H, ix, p. 172 (Allen). Case II	IV*a*	10 – 2 = 8 (2 *ob.* young)	2 or 3
Ibid., xvii, p. 366. Case 118 (Nolte)	III*a*	8	2
	b	4	2
Liebreich, *Arch. Gen. de Med.*, 1861. Case 2	II*a*	6	3
Gonin, *An. d'Oculist*, pp. 125, 101 (1901), and 128, 91, and 128 (1902). Case 1. Family D.)	II	7	4
Webster, *Trans. Am. Oph. Soc.*, ii, p. 504. Cases 20 to 23.	II	7	3
Coleman, W. F., *Amer. Practitioner*, 1889, p. 49.	II	13	5
Unpublished—(Mr. Fisher's case), this lecture, Fig. 39	V	7	2

Summary.

Total.	Normal.	Affected.
199	113	86
(100)	(57)	(43)

The above 22 cases contain 31 sibships available for the foregoing tables. Thirty of these sibships may be classed into three groups, showing respectively (*c*) almost every individual affected, (*a*) nearly one half, (*b*) nearly one quarter. Only one, Fig. 36, III*a*, with 4 affected out of 11, is widely inconsistent.

(*c*) Nearly all affected.

R.L.O.H., xvii, p. 17, *et seq.*

Case.	Total.	Affected.
15. IV*b*	1	1
15*b*. III	8	7
36. V*c*	4	3
Totals	13	11

(*a*) Nearly one half affected.

Ibid.

Case.	Total.	Affected.
15. IV*a*	7	3
15*a*	4	2
16	5	3
18	4	2
20 III*a* + *b*, *a* = 8 and 3; *b* = 13 and 6	21	9
25	6	3
26	7	4
27	4	2
	58	28

Ibid.

Case.	Total.	Affected.
32	5	3
33	9	4
This Lecture, 37, III*a*	8	3
Liebreich, *Arch. Gen. de Med.*, 1861, Case 2, II*a*	6	3
Gonin, *An. d'Oc.*, 125 and 128 (1902). Family D. II	7	4
Webster, *T.A.O.S.*, ii, 504, Cases 20 to 33, II	7	3
Coleman, *Amer. Pract.*, 1889, p. 49, II	13	5
R.L.O.H., xvii, p. 366, Case 118, III*b*.	4	2
	59	27
Totals	117	55

(*b*) Nearly one quarter affected.

	Total.	Affected.
R.L.O.H., *ibid.*, Fig. 38	4	1
„ „ „ 40	4	1
This Lecture, Fig. 37, III*b*	4	1
„ „ 36, IV*a*, V*a*, *b* and *d*, all same proportions	23	6
This Lecture, Fig. 39, V.	7	2
	42	11
	Total.	Affected.
R L.O.H., *ibid.*, p. 366, Case 118, III*a*	8	2
„ „ vol. ix, p. 172, 2, IV*a*	8	2 or 3
	16	4 or 5
Totals	58	15 or 16

(F) *Diseases Allied to Retinitis Pigmentosa.*

Reference.	Generation and sibship (childship).	Persons counted; affected and normal. ●+○	Number affected. ●
Atrophia gyrata choroidæ et Retinæ (Fuchs).			
R.L.O.H., xvii, pp. 369–373.			
Case 125	—	10	3
Ibid. „ 127	II	5−2=3 (2 *ob.* inf'cy)	1
„ „ 129	II	10−1=9 (1 *ob.* inf'cy.)	4
Congenital Absence of Choroid.			
R.L.O.H., xvii, pp. 373–377.			
Case 131	—	9	2
Ibid. „ 133	—	8	3
„ „ 134	—	11−3=8 (3 *ob.* inf'cy)	1

Reference.	Generation and sibship (childship).	Persons counted; affected and normal. ●+○	Number affected. ●
Retinitis punctata albescens.			
R.L.O.H., xvii, pp. 377–393.			
Case 141	—	5	4
Ibid. „ 142	—	10−4=6 (4 died inf'cy)	3
„ „ 143	II*a*	2	1
„ „ 144	IV	7−1=6 (1 *ob.* inf'cy)	2
„ „ 145	—	8−6=2 (6 *ob.* inf'cy)	2
„ „ 146	VI	10−2=8 (2 *ob.* inf'cy)	2
„ „ 150	—	5	4
Liebrecht's case: diagnosis doubtful.			

Summary.

Total.	Normal.	Affected.
81	50	31

(G) *Congenital Night-blindness without Changes—Continuous Descent; Both Sexes Affected. Cunier Group.*

Reference.	Generation and sibship (childship).	Persons counted; affected and normal. ●+○	Number affected. ●
R.L.O.H., xxvii, pp. 401–405.			
Case 152	II	10	5
	III	3	2
	IV*a*	5−2=3 (2 *ob.* inf'cy)	2
Ibid. „ 153	IV*a*	4	2
	b	3	2
	c	3	2
	d	7	4
	V*e*, *f*	6	2

Reference.	Generation and sibship (childship).	Persons counted; affected and normal. ●+○	Number affected. ●
Ibid. Case 154	III	5	3
„ „ 156	III	3	1
	IV	7	3
	V*a*	5	2
	b	4	3

Summary.

Total.	Normal.	Affected.
63	30	33

(H) *Congenital Night-blindness without Changes—Discontinuous Descent.*

Reference.	Generation and sibship (childship).	Persons counted; affected and normal. ●+○	Number affected. ●
Both Sexes Affected.			
R.L.O.H., xvii, pp. 406–410.			
Case 158	II	10	5
Ibid. „ 160	II*a*	8	3
„ „ 161	II	13	3
„ „ 162	II	5	2
	III	1	1
„ „ 164	—	6	2
Only Males Affected.			
Ibid., pp. 410–422.			
Case 166	III	6, 5♂ 1♀	3
„ „ 168	III*a*	9, 3♂ 6♀	3
„ „ 169	III	4, 2♂ 2♀	1
	IV*a*	5, 3♂ 2♀	3
	b	4, 2♂ 2♀	0
	V*c*	2, 1♂ 1♀	1
	d	9, 5♂ 4♀	2
	e	8, 4♂ 4♀	3
	f	1♂	1
	VI*a*	2, 1♂ 1♀	1
	b	7, 4♂ 3♀	3
	c	3, 2♂ 1♀	2
„ „ 170	III	7, 3♂ 4♀	2
	IV*a*	4−1=3 ♂ (1♂ *ob.* inf'cy)	1
	b	4, 2♂ 2♀	1
	c	3, 1♂ 2♀	1
„ „ 171	III	5, 3♂ 2♀	3
	IV*a*	8, 4♂ 4♀	2
Ibid. Case 171	IV*b*	1♂	1
	c	8, 4♂ 4♀	1
	V*a*	2, 1♂ 1♀	1
	c	2♂	2
	d	7, 3♂ 4♀	1
	VI*a*	6, 3♂ 3♀	1
„ „ 173	III*a*	2♂	2
	b	4, 3♂ 1♀	2
	c	2♂	2
	V	3♂	1
„ „ 175	II	11−5=6 (5 *ob.* young) 2♂ 4♀	2
	III*a*	2♂	1
	b	3♂	2
„ „ 176	IV*a*	10−4=6 (4 *ob.* inf'cy) 3♂ 3♀	3
	b	6♂	3
	c	7♂	3
	d	3♂	2
„ „ 177	IV*a*	5, 3♂ 2♀	2
„ „ 178	III*a*	2♂	2
	b	5, 3♂ 2♀	2
	c	8, 5♂ 3♀	4
	d	7, 3♂ 4♀	3
	e	7, 3♂ 4♀	2
	f	5, 3♂ 2♀	2
	IV*a*	4, 2♂ 2♀	2
	b	8, 2♂ 6♀	2
	c	2♂	1

Summary.

Total.	Normal.	Affected.
260	159	101
(100)	(64)	(36)

(1) *Leber's Disease* (*only Males Affected*).

Reference.	Generation and sibship (childship).	Persons counted; affected and normal. ●+○	Number affected. ●
Published cases:			♂ ●
87. Pufahl .	—	6, 3♂ 3♀	3
89. Fuchs .	—	8, 4♂ 4♀	4
90. „ .	I	6, 2♂ 4♀	2
	II	5, 4♂ 1♀	0
94. Schlüter .	II*a* + *b*	7, 4♂ 3♀	4
	III*a* + *b*	5, 3♂ 2♀	3
96. „ .	II	4, 2♂ 2♀	1
102. E. N. (publ. by Habershon, *T.O S.*, viii).	II	11, 8♂ 3♀	5
103. E. N. *Ibid.*	II*a*	5, 2♂ 3♀	2
105. E. N. *Ibid.*	—	6, 3♂ 3♀	2
107. Browne .	—	5, 3♂ 2♀	3
45. Gould .	III	5, 2♂ 3♀	2
	IV*a*	10−4=6 (4 *ob.* young) 4♂ 2♀	1
	V*a*	8−4=4 (4 *ob.* young) 3♂ 1♀	3
	b	8−1=7 ♂ (1 *ob.* young) No ♀	1
	c	4−1=3 ♂ (1 *ob.* young) no ♀	3
	VI*a*	8−3=5 (3 *ob.* young) 3♂ 2♀	1
Published cases:			
115. Ogilvie .	II*a*	16−10=6 (10 *ob.* young, 5♂ 3♀) living 3♂ 3♀	3
46. Snell . .	II*a*	3, 1♂ 2♀	1
	III	9−2=7 (2 *ob.* young) 2♂ 5♀	2
120. „ . .	II	7−2=5 (2 *ob.* young) 4♂ 1♀	3
136. Leber. .	III, *a*, *b*, *c*	9, 6♂ 3♀	4
139. Westhoff .	II	4, 3♂ 1♀	2
	III*a*	4, 3♂ 1♀	3
	IV	6, 5♂ 1♀	4
143. E. N. . .	II	8, 6♂ 2♀	4
	III	3, 1♂ 2♀	1
144. „ . .	II	6, 2♂ 3♀ 1, ? sex	2
	III	16−12=4 (12 *ob.* infancy) 2♂ 2♀	2
47. Hancock .	III*a*	8, 3♂ 5♀	3
	IV*a*	6, 4♂ 2♀	1
	b	6, 3♂ 3♀	3
	c	2♂ no ♀	2
	V*a*	1♂ no ♀	1

Leber's Disease (*only Males Affected*)—continued.

Reference.	Generation and sibship (childship).	Persons counted; affected and normal. ●+○	Number affected. ●
Published cases:			
147. Lawford .	II*a*	7, 3♂ 4♀	3
149. Schilling .	—	6, 5♂ 1♀	5
79. Leber. .	—	6, 5♂ 1♀	5
152. Leitner, Case 1 (second paper).	II	4, 3♂ 1♀	3
	III	4♂ no ♀	3
154. Posey .	II	13−3=10 (3 *ob.* young) 4♂ 6♀	1
	III*a*	5, 2♂ 3♀	1
48. Klopfer .	VIII	3, 2♀ 1♀	1
	IX*a*	6, 2♂ 4♀	1
	b	3♂ no ♀	3
155. Leitner, Case 1 (first paper).	III*a*	6, 3♂ 3♀	3
	b	7, 4♂ 3♀	1
	c	9, 2♂ 7♀	1
156. Leitner (Case 2, second paper).	II*a*	5, 2♂ 3♀	2
163. Heinsberger	—	6, 4♂ 2♀	3
166. Raymond .	III*a*	5, 3♂ 2♀	1
168. Costa . .	III*a*	4, 3♂ 1♀	2
	b	2, 1♂ 1♀	1
	IV	2, 1♂ 1♀	1
171. Batten .	I	11, 6♂ 5♀	1
	II*a*	7, 4♂ 3♀	1

Reference.	Generation and sibship (childship).	Persons counted; affected and normal. ●+○	Number affected. ●
Published cases:			
171. Batten .	II*b*	7, 3♂ 4♀	2
83*a*. Batten .	II	10, 6♂ 4♀	4
84. Vossius .	IV*a*	6, 4♂ 2♀	2
86. Buisson .	III*a*	5, 2♂ 3♀	2
23. Haswell .	III*a*	9, 7♂ 2♀	6
	IV*a*	8, 1♂ 7♀	1
24. Taylor .	III*a*	12−1=11 (1 *ob.* inf'cy) 6♂ 5♀	4
25. Sym . .	II*a*	5, 3♂ 2♀	3
42. Strminski .	III	7, 5♂ 2♀	5
49. E. N. . .	II*a*	5, 4♂ 1♀	2
91. Raymond .	II	10−4=6 (4 *ob.* young) 3♂ 3♀	3
	III*a*	2♂ no ♀	1
	b	3, 1♂ 2♀	1
85. Usher .	III	11, 8♂ 3♀	3
	IV	3♂ no♀	2

Summary.

Total.	Normal.	Affected.
402	237	165
(100)	(59)	(41)

Leber's Disease—Males and Females Affected.

Reference.	Generation and sibship.	Persons counted (total).	Males.	Females.
77. Leber .	—	6, 3♂ 3♀	2	1
78. „ .	—	4, 1♂ 3♀	1	1
49. Norris .	IIIa	2♂ no ♀	1	0
	b	5, 2♂ 3♀	2	1
	IVa	4, 2♂ 2♀	1	1
	b	7, 4♂ 3♀	4	3
98. Story .	—	8, 4♂ 4♀	4	1
99. Holz .	—	5, 2♂ 3♀	1	2
112. Despagnet	IIIa	7−2=5 (2 *ob.* young) 4♂ 1♀	3	1
113. Somya .	IIa	5, 3♂ 2♀	2	1
116. Batten .	III	4−1=3 1♂ 2♀	1	1
117. Snell .	—	8, 6♂ 2♀	3	1
140. E. N. (Wilson, etc. unpublished	IIIa	10−6=4 (6 *ob.* young) 1♂ 3♀	1	2
141. E. N. (Donovan) unpublished	IIIa	14−10=4 (10 *ob.* y'ng. 1♂ 3♀	1	1
142. E. N. (Laxford) unpublished	IIIa	7, 5♂ 2♀	3	1
50. Knapp .	III	8−1=7 (1 *ob.* young) 4♂ 3♀	2	2
	IV	6, 5♂ 1♀	3	0

Reference.	Generation and sibship.	Persons counted (total).	Males.	Females.
52. Doyne (Perrin) unpublished	III	4, 3♂ 1♀	1	1
	IV	5−2=3 (2 *ob.* inf'cy.) 2♂ 1♀	2	1
51. Matthieu	IIa	5−1=4 (1 *ob.* inf'cy.) 1♂ 3♀	1	1
	IIIa	14−7=7 (7 *ob.* young) 4♂ 3♀	1	1
162. Lauber .	IV	14−6=8 (6 *ob.* young) 4♂ 4♀	4	1
159. Gallemaerts	IIa	5, 3♂ 2♀	2	1
128. Leber .	—	5, 2♂ 3♀	2	1
153. Leitner, Case 2 (first paper).	II	6, 1♂ 5♀	1	1
	IIIa	5, 4♂ 1♀	1	0
	b	2, 1♂ 1♀	1	0
	c	6, 3♂ 3♀	1	0

Summary of this Table.

Total.	Normal.	Affected.
145	65	80
(100)	(45)	(55)

Summary of both Tables.

Total.	Normal.	Affected.
547	302	245
(100)	(55)	(45)

(J) *Proportion of Females Carrying Disease in Certain Sex-limited Affections.*

In a disease transmitted only by unaffected females the number of sisters in any childship who carry it can, with our present knowledge, be known only if they all have children. The following are the only examples I have been able to find, and even in them the evidence must be regarded as incomplete for such of the sisters as had very few children:

(1) Discontinuous retinitis pigmentosa: Fig. 36, IV*b*,* contains 5 sisters, 1 of whom dies single; of the others 2 have 12 children in all, some of whom have the disease; the other 2 have 4 children in all (only 3 of these are shown in the Figure), none of whom have the disease.

(2) Discontinuous night-blindness: Fig. 42, IV*a*, contains 4 sisters; 2 of them have 9 children in all, some affected; the other 2 have 4 in all, all normal.

(3) Discontinuous night-blindness (*R.L.O.H.*, xvii, p. 419: Fig. 175), II, contains 4 sisters; 2 of them have in all 5 children, some affected; the other 2 have in all 3 children, all normal.

(4) Discontinuous night-blindness (*ibid.*, xvii, p. 422: Fig. 178, III*b*), contains 2 sisters; 1 has 4 children, some affected; the other 2 children both normal.

(5) Leber's disease (this Appendix: Fig. 108, III*a*), contains 2 sisters, both of whom had affected issue. Note that of their 7 brothers 6 had the disease.

(6) Leber's disease (*ibid.*: Fig. 94), the two small childships II*a* and *b*, contain 3 females, 2 of whom married, and both had some affected children.

(7) Leber's disease (*ibid.*): Fig. 143, II, contains 2 sisters, of whom one certainly bore affected issue.

(8) Leber's disease (*ibid.*): Fig. 166, III*a*, contains 2 sisters, of whom one bore three children, one of them affected; the other had an only child who was affected.

In these eight instances we have 24 sisters, of whom 21 certainly had children (1 died childless and 2 others appear to have been unmarried at date of record). Of these 21, 13 had amongst them rather more than 51 children (exact number in one case not given), containing 18 affected. The remaining 8 had amongst them only 14 children, all normal.

* IV*b*.—The letter *b* signifies the second eligible childship in Gen. IV counting from the left; the first is *a*. These letters are not marked on the Figure. The same explanation applies to the other relevant Figures.

APPENDIX II.

Sex in Lamellar Cataract, whether Hereditary or Sporadic (including Discoid Cataract).

[The following returns have been kindly supplied to me by various colleagues and friends.]

Source.	Males.	Females.	Total.	Source.	Males.	Females.	Total.
Moorfields Hospital, over about ten to fifteen years.	405	195	600	Oxford (Mr. Doyne) .	36	29	65
St. Thomas's Hospital, since 1878.	60	30	90	Birmingham, Queen's Hospital (Mr. Priestley Smith).	57	38	95
St. Bartholomew's Hospital, twenty-four years.	113	65	178	Birmingham Eye Hospital, four and a half years.	18	9	27
St. George's Hospital, about twenty years.	29	18	47	Cases from forty, published and unpublished.	140	130	270
London Hospital, the last few years.	18	10	28	Cases seen in private practice, seven separate returns.	58	57	115
Dublin (Sir H. R. Swanzy), ten years.	45	18	63		4	2	6
Aberdeen (Mr. C. H. Usher).	32	33	65		8	6	14
Manchester (Mr. Hill Griffith) four years.	58	41	99		6	5	11
					12	7	19
					28	5	33
					39	23	62
				Totals. .	1166	721	1887

Sex in Congenital Cataracts other than Lamellar.

Source.	Males.	Females.	Total.	Source.	Males.	Females.	Total.
Moorfields Hospital (partial return only).	58	38	96	Birmingham, Queen's Hospital (Mr Priestley Smith).	25	20	45
St. Bartholomew's Hospital, twenty-four years.	22	18	40	Birmingham Eye Hospital (Mr. Eales), five years.	45	55	100
Dublin (Sir H. R. Swanzy), ten years.	18	8	26	Cases from various published pedigrees.	82	82	164
				Totals. .	250	221	471

APPENDIX III.

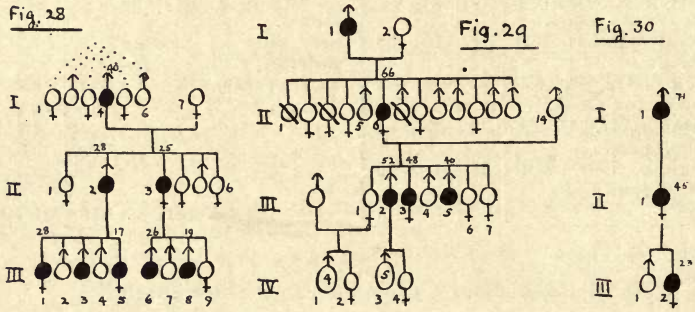
Glaucoma.

The paper by Lawford in *R.L.O.H.*, xvii, p. 57 (1907), "Examples of Hereditary Primary Glaucoma," contains particulars of twenty-four families in which the disease prevailed, and a list of nineteen references to the literature. Six of the cases are new, eighteen had been published before.

Anticipation was well marked in at least half of the series, *viz.*, Cases 1, 3, 6, 7, 8, 10, 11, 13, 14, 16, 17, 24, taking them serially as they come in Lawford's paper. The following seven of these were shown in pedigree form at the lecture.

Fig. 28 (Lawford, Case 7, from Lucien Howe) : I, 4 affected at about 40, and became blind; II, 2 affected at 28; II, 3 at 25; III, 1 at 28; III, 3 probably about the same age; III, 5 at 17; III, 6 at 26; III, 8 at 19.

Fig. 29 (Lawford, Case 1) : I, 1 blind from "amaurosis" (? glaucoma simplex) for some years before death at 85; II, 6, double, quiet glaucoma at 66, operated upon, died at 71; his wife (II, 14) died at 63; 3 of his



siblings died in infancy, 2 others (II, 5 and 9) died as adults, all the others living and reported to see well; III, 1 to 7 issue of II, 6 and 14, aged, at record, from 53 to 36, and all except III, 1 examined by author; III, 3 and 5 got glaucoma simplex at 48 and 40 respectively, and III, 2 had, at 52, signs of the incipient disease. In IV all are reported to see well, the eldest of IV, 1 being 27, and of IV, 3, 29.

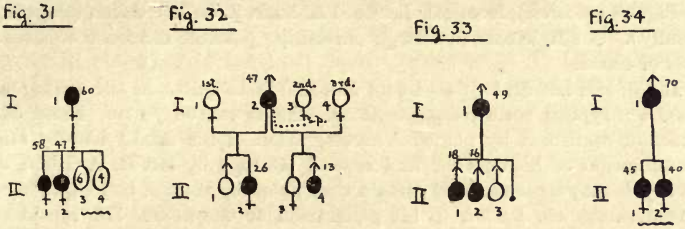
Fig. 30 (Lawford, Case 8 : Nettleship, *The Ophthalmoscope*, September and October, 1906). I, 1 affected at about 71; II, 1 at 45; III, 1 at 23.

Fig. 31 (Lawford, Case 3) : I, 1 blind at 60, almost certainly from glaucoma, died at 68; II, 1 attacked at 58; II, two years younger, attacked at 47; II, 3, 6 other living siblings who see well; II, 4, 4 who died.

Fig. 32 (Lawford, Case 14) : I, 2 glaucoma at 47; of his 2 children by first wife, II, 2 had glaucoma at 26, and of the two by third wife, II, 4

glaucoma at 13; second wife (I, 3) childless. This case also shows coincidence of high myopia and glaucoma in II, 4.

Fig. 33 (Lawford, Case 15, Mules, *O.R.*, ii, p. 48, 1883): I, 1 glaucoma



simplex at 49; II, 1 the same at 18; II, 2 at 16: II, 3 at 15 had increased tension, but no other signs.

Fig. 34 (Lawford, Case 24; Jacobson, *A.f.O.*, 1886, iii, p. 96): I, 1 glaucoma simplex at 70; II, 1 at 45, and II, 2 at 40.

APPENDIX IV.

Retinitis Pigmentosa.

The principal pedigrees upon which I base what is said at p. xcv *et seq.* of the text as to continuous and discontinuous descent in different families may be found in *R.L.O.H.*, xvii, pp. 7–17 and 360 for continuous descent, and at pp. 18–24 and 26–31 for discontinuous descent. I have gone over these again carefully, and find no errors except that in Fig. 33 Gen. I should be omitted, there being no information.

Discontinuous descent of retinitis pigmentosa side by side with continuous descent of lamellar cataract is shown in a pedigree published in *T.O.S.*, xxviii, p. 226 (1908). In the text of the lecture the two parts of this genealogy were treated separately, the part containing the cataract cases being shown in Fig. 12, and that containing retinitis pigmentosa in Fig. 36.

The details of the cases shown by Figs. 37, 38, and 39 are as follows:

Fig. 37 (p. xcvi), sent by Mr. C. H. Usher (Rowand family), 1909. I, 3 was invalided from the Army as a young man for 'moon-blindness," and was told it would get worse; could see well in the day, but not in the evening; got steadily worse, was quite blind at 50, and died at 70.

I, 1, 2, and 4 all good sight. II, 1 and 5 both good sight. III, 8, æt. 36 years, typical advanced retinitis pigmentosa; has one child with good sight (IV, 4). III, 7, æt. 38 years, conditions much like III, 8; hearing very quick; has four sons, all living, and one daughter, who died lately, all with good vision (IV, 2 and 3). III, 9, æt. 34 years, conditions as in the other two; married fourteen years, no issue. III, 12, æt. 50 years, nearly blind of retinitis pigmentosa, a drinker, and has been under care for delirium tremens; twice married; no issue by first wife, but by

second has five or six children, in one or two of whom sight is bad both day and night. III, 4 died in infancy. III, 5 at 14. III, 6 is 40; has good sight and three normal children. III, 10 and 11, and the child, IV, 5, all see well.

Fig. 38 (p. xcvii), from Mr. Lawford and Mr. E. Collier Green (Paynter family). A single case in a large childship; possible influence of severe loss of blood.

III, 3, Mr. Lawford's patient at Moorfields Hospital in the spring of 1909 for typical retinitis pigmentosa. He is æt. 38 years. From his account, confirmed by personal investigation of his family history and examination of his mother and several siblings by Mr. E. C. Green, of Derby, it may be considered certain that no other cases of bad sight or of degeneracies are known in his generation or the next. He considers his sight to have been failing ten or twelve years, but can give no precise date, and did not himself connect it with the hæmorrhages of which he gives a history. When 26, a railway porter, he bled violently from the nose one day from 9 a.m. till noon, and was plugged at St. Bartholomew's Hospital. When 33 (five years ago) was operated at the Great Northern Hospital for "appendicitis," and says that about two weeks after the operation he vomited a quantity of blood. Again a year ago he was in bed for six weeks, and passed blood both from the bowel and bladder. The history of the epistaxis is clear enough, but his statements as to the internal hæmorrhages are, of course, of less value. Has not had typhoid or other infectious illnesses to his knowledge, and denies venereal disease of any kind, and shows no signs of congenital syphilis. Married ten years; two children, of which IV, 2 died at 13 months and would now be 8; IV, 2 living, æt. $2\frac{2}{12}$ years. Mother (II, 2), æt. 60 years, examined by Mr. Green, and found normal; by first husband (II, 3), who died at 52 from an accident, sixteen conceptions (III, 1 to 16), of whom III, 1, æt. 40 years, and III, 9 and 10 (the latter the youngest living, æt. 23 years) have been examined by Mr. Green and found normal. III, 2, 6 and 11 to 15 miscarriages (seven in all), and III, 16 died of measles at 9 months. IV, 1, 8 children (3 boys, 5 girls) of III, 1, æt. from 17 to 3 years; 7 are living, and were examined by Mr. Green and found normal; the boys are the first, eighth, and fifth; the latter died of "brain fever" after an accident three years ago; the girls are Nos. 2, 3, 4, 6, and 7. The other sixteen (IV, 4 and 5) and their parents are scattered, and could not be seen, but all are confidently reported to see well. II, 2 had no issue by her second husband. Her brother (II, 1) married, but had no issue. I, 1 living; I, 2 dead; sight good in both. No consanguinity.

Fig. 39 (p. xcvii), from Mr. Herbert Fisher. The family records have been accurately kept for many generations. The figure shows only the parts of the family tree that bear upon the occurrence of retinitis pigmentosa and deafness.

V, 5 æt. 45 years, well-marked typical retinitis pigmentosa, and is moderately deaf. V, 8 deaf, but good sight; V, 4 died of phthisis as a young man; V, 3, 6, 7 and 9 normal. No other cases known of bad

sight like V, 5, but a vague history of defective sight in IV, 12 and III, 10. Clear history of deafness from early life in II, 6, IV, 7 and 11, V, 8 and 10; the deafness has varied in severity in the different persons, very bad in II, 6 and IV, 11, moderate in the others. VI, 2 has had attacks of mania; her brother, a medical man, says she resembles her aunt, V, 5, closely in some respects. VI, 6 died in infancy "from some defect in the larynx," and VI, 7, the two children of V, 8, also died in infancy. IV, 7 and his wife, IV, 3 were second cousins, but the consanguinity was from another stock in which there are no known cases of blindness or deafness.

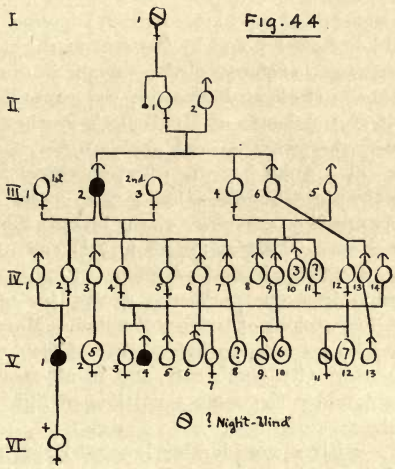
APPENDIX V.

Night-Blindness without Changes.

(*a*) The cases used, being all I have been able to find either in the literature or amongst my own notes, are given in *R.L.O.H.*, xvii, pp. 401 to 426, and there numbered Cases 151 to 190 (1908).

(*b*) Mr. W. J. Cant's case, Case and Fig. 44.—Night-blindness without visible changes affecting myopic males.

In this small pedigree only three or four cases are known. Two of



them have been seen and examined with care, and I therefore record the case fully.

I, 1 was a woman who lived to be 90; she became blind in her old age, but there is nothing to show that she had night-blindness.

She had at least one daughter, II, 1, but whether there were other children is not known. II, 1 had three children, no more.

The first-born, III, 2, is reported by his daughter to have been "very short-sighted and night-blind, and had always to be led about after dusk all his life"; as he lived to be 76, and is never known to have worn reading spectacles, he was probably myopic. He had a sister and a brother (III, 4 and 6) who had perfect vision until they died; both left children and grandchildren. Of the latter, two had some affection of sight, but no one knows whether they were night-blind or not (see below); all their other descendants in IV and V are normal.

He (III, 2) married twice, there being no consanguinity between him and either wife or between the wives. By the first he had an only child ♀ (IV, 2), with good sight, who had an only child (V, 1, illegitimate), now aged thirty-five and night-blind; his only child (VI, 1) is normal. By his second wife, III, 2 had 5 children (IV, 3 to 7) all with good sight, three ♂, two ♀. One of the daughters (IV, 4), who died in 1908, left a son who is night-blind (V, 4) and a daughter (V, 3) with normal eyes. Of the numerous other grandchildren of III, 2, none are night-blind, but it is noteworthy that the other female who might transmit (IV, 5), has had only one child.

Description of the Cases.

III, 2 a compositor, who died at 76, is reputed to have been always unable to see at night but to have had no defect in the day; his daughter, IV, 4, remembers (speaking in 1907) having often in former years had to lead her father home by the arm at night; he never wore any spectacles, and was therefore probably myopic in some degree.

V, 1, æt. 35 years, a clerk at Doncaster, was examined by Mr. C. H. Usher and myself at the house of Mr. Usher's brother in Lincolnshire in 1908. Has been short-sighted and unable to see at night as long as he can remember; as a small boy when first at school he could not see the blackboard; the night-blindness has got no worse. Has never had glasses, and the progress or otherwise of the myopia therefore cannot be ascertained; refraction now, estimated about 7 D. and 10 D. in R. and L. at posterior pole, decidedly less at periphery; fundus of medium complexion and normal in every particular except for moderate myopic crescents. Black hair, colour of irides not noted. Married eight years, one child only. The tests as to light sense defect were necessarily inexact but were made with much care, and in all cases were compared with our own sight under the same conditions of light, but his myopia was not corrected.

As to reading:—with a considerably lowered light, he was unable to read print with his myopia uncorrected, which I (E.N.) could read perfectly with + 4 or + 5 D.; but in good lamp-light he read J. 1 easily. When shown a screen and a bed-cover, each with large patterns of different but somewhat sombre colours, he required much more light than we did to recognise the pattern, and this at his own normal far point. No defect of Fs. could be discovered, but we noticed that when seeking to see an object beyond his far point, *viz.*, a picture, or the pattern on the

screen, he always looked considerably above the object, *i. e.*, he used the retina a little above the Y.S. He was then tested in the garden in brilliant moonlight, and the following notes made: he could not see a white handkerchief on the grass only a foot from him, although it was visible to all of us at many yards off; he could not see the white cuff of his own shirt when his coat sleeve was drawn up; he was quite unable to see a number of flowers that were easily visible to the rest of us; finally he was quite unable to find his way about the lawn (a flat one) without a guide, and on turning to the house said that the lighted window was the only thing by which he could at all guide himself; and it was obvious that if there had been any pit or obstacle on the ground he would have walked into it unless guided. The whole result was very striking, and certainly not to be explained merely by the uncorrected myopia. Married eight years, one child, æt. 8 years (VI, 1), seen and found to have H. 2 D, with normal fundus, perfect sight, and no night-blindness.

V, 4 began glasses at four years old, and was first seen by Mr. W. J. Cant in 1889, *viz.*, when from five to six years of age, and found to be using − 9 D. spectacles; Mr. Cant gave him − 6 D. In April, 1904 (æt. about 10 years) the R. was found to be divergent and somewhat amblyopic, V. with correction being only $\frac{6}{24}$ against $\frac{6}{12}$ with the L., and he had difficulty in maintaining fixation with R.; it was probably then that his present full correction was ordered. There is no further record until the early part of 1908 (æt. 14 years), when Mr. E. C. Clements and Mr. Cant made a careful examination, with the following results: R. − 10 D. $\frac{6}{12}$; L. − 9 D. sph. with − 1·5 D. cyl. $\frac{6}{9}$ partly; is already wearing glasses of this strength. When the illumination is reduced to half light, V. with correction equals only $\frac{3}{36}$, and with one quarter illumination only $\frac{6}{60}$, and with the window-blind drawn still further down he was unable to see a piece of white paper 10 in. (25 cm.) square at 6 ft., even when it was moved about. Fields for white; L. normal in full light, much reduced in the same half and quarter light; when the blind was drawn more than three quarters down the fixation object was invisible to him even when $\frac{1}{2}$ in. square; R. (amblyopic eye) smaller for full light than L., and shows similar further contraction in lowered light. Fundus perfectly healthy in appearance in every detail, except for ordinary sharply defined crescents from one quarter to one third the width of O.D.; especially, retinal vessels of full size and no trace of retinal pigmentation.

His mother noticed that his sight was not right before he was a year old, and that when between two and three he could not see his toys if the light was at all bad, but had to grope for them.

When Mr. C. H. Usher and I saw him (October 3rd, 1908) we found him a tall, narrow-chested boy, 5 ft. 6 in. high, of between 14 and 15 years, with, as already noted, perfectly normal fundi; by estimation the myopia was much less at the periphery than at posterior pole of globe; choroids rather fair. Various comparative qualitative tests applied whilst wearing his correction, such as a square of white paper several inches in the side viewed under different degrees of illumination, showed repeatedly

that his light-minimum was much higher than ours, and that he required longer than we did in order to see the object even when the light was enough (*viz.*, slow adaptation); and with light below his minimum a slight increase at once made the object visible to him (this also shows slow adaptation). Fields to rough hand tests did not show contraction. He always takes his sister's arm when out with her in the dusk. At home he often knocks against a certain door-prop which his sister says no one else would do.

V, 3, only sister of the last, æt. about 20 years, a school teacher, not myopic, fundus perfectly normal.

V, 9, said to have been "very short-sighted, held his book very close," and his aunt, IV, 4, who knew him, wrote that "she thought he was afflicted in much the same way as her son," V, 4; he did not use spectacles; died at 25. He had about six siblings, who all saw quite well.

V, 11 said never to have had good sight, and eventually went quite blind, but no particulars are known. She is dead. She was one of the seven or eight children. She did not wear glasses.

V, 13 known to have good sight.

IV, 4, who died during 1908, had perfect sight, as has her husband, IV, 14.

III, 4 and 6 had perfect vision.

No consanguinity between IV, 4 and 14.

Case 44*a* (no figure).—By a curious coincidence another family with the same complaint lives in the next village to V, 4 of the case just narrated. The two families are not related in any way on either side; the former came from a distance in recent years, the latter has been settled as farmers at or near Navenby for a long time.

This second family could not be fully searched out; the information obtained is given for what it is worth.

III, 1 and 2 were first cousins and I, 1 was the grandfather of one of them and he became blind, probably from cataract, in old age, and died recently (1907 or 1908) at 80. II, 1 is living and sees well; her husband, who also had good sight, died in middle age. They have 5 children, and I believe there were no more.

III, 1, æt. 24 years, very poorly educated on account of his bad sight, is said by his mother to have been very short-sighted and night-blind since early childhood. When examined (October 3rd, 1908) we estimated his myopia at about 10 D. by direct ophthalmoscopic measurement, and found the retinal vessels normal and no fundus changes, except moderate crescents. With his spectacles on his sight was conspicuously defective for objects 4m. to 5m. off in a dim light (partially darkened passage in his own house); without glasses he only read J. 4 word for word, but as he was almost illiterate this test was inconclusive; the Fs. to rough hand test seemed full. His mother said that he always had to be led home from church after evening service.

III, 2, æt. 17 years, now has about 3 D. of myopia, and did not show any shortness of sight till she was about 13. Nothing was said about night-blindness in her; fundus normal.

III, 5, æt. 13 years, is just like III, 1 in his sight; has been very short-sighted and blind at night since early childhood; now has about 10 D. of myopia, with moderate crescents, but no other fundus changes; read J. 3 and 4 fluently both with and without her glasses. Like her brother, III, 1, she has always to be led home from evening church. The other two have no defect. There is a history of "blindness" in a half-cousin, but no particulars were to be had.

APPENDIX VI.

Leber's Disease.

(*a*) *Abstracts of Published Cases in Chronological Order beginning with v. Graefe's case,* 1858, *to which are added some hitherto unpublished Cases communicated by friends or taken from my own note-books.*

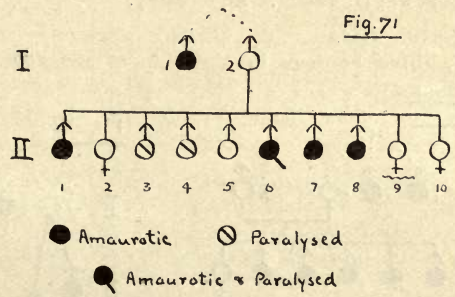
The references down to 1899 are taken chiefly from Habershon's paper in *T.O.S.*, viii (1888), and Hormuth's *Dissertation* published in 1900 (title given on p. cxxxvii). The particulars of each case are also in many instances taken from Hormuth's tables. When, however, his abstract of a case seemed unsatisfactory reference was made to the original; but such reference has seldom led to any correction of Hormuth's rendering. All cases consulted in the original are marked with a star (*).

1858. Case 70. v. Graefe, *A.F.O.*, iv, 2, p. 256.

Male, onset at twenty years of age; failure progressed three months, both eyes; recovered to reading small print in four weeks; no ophthalmoscopic note. His brother, onset æt. 20 years, J. 20, no improvement; fundus normal three years later. Third brother, also attacked in same way at nineteen. Parents normal.

1862.* Case 71. Sedgwick, *Med. Times and Gaz.*, i, p. 309.

Usually quoted as Leber's disease, but the coincident family paralysis



and absence of ophthalmoscopic examination exclude precise diagnosis. I, 1 blind from "amaurosis" at about 55. II, 1 amaurotic both eyes at 56; 2, living, æt. 63 years, good eyes; 3, died paralysed but good vision,

at 56; 4, living at 60, paralysed, good sight; 5, living, æt. 56 years, good sight, no mention of paralysis; 6, amaurotic, both eyes, at 48, died paralysed; 7, left eye amaurotic at 46; 8, amaurotic both eyes at 42, died, but age and cause not given; 9, normal, place in childship not noted; 10, normal, æt. 38 years.

1865. Case 72. v. Graefe, *K.M.f.A.*, iii, p. 222.

Two brothers, both attacked at 23, in both eyes; central scotoma, moderate optic atrophy in one patient, no note in other; no recovery. Family history negative.

1867.* Cases 73–76. Mooren, *Ophthalmiatrische Beobachtungen*, p. 305.

Three brothers and an uncle, loss of central V. with slight neuro-retinitic appearances. *Ibid.*, three brothers; *ibid.*, two brothers; *ibid.*, two brothers. All attacked between 18 and 23. Some improvement in early period of treatment in all.

1871. Case 77. Leber, *A.f.O.*, xvii, 2, p. 249, family II. Two brothers and a sister affected out of six. Parents normal. II, 1 affected at 17,

Fig. 77

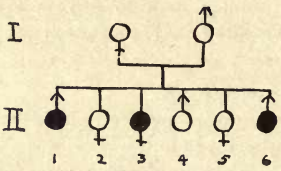
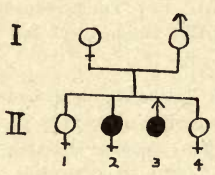


Fig. 78



seen at 30. II, 3 affected at 28, and II, 6 at 19, both seen at early stage. All three recovered after some months from finger V. to J. 1

1871. Case 78. *Ibid.*

Family III. A brother and sister affected out of four. Parents normal. II, 2 affected at 27; II, 3 at 21. No recovery.

1871. Case 79. *Ibid.*

Family I. Five brothers in a sibship of six, and two maternal

Fig. 79

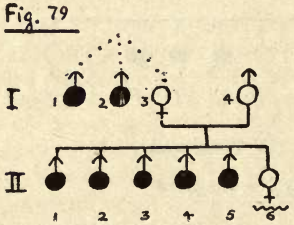
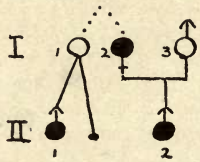


Fig. 80



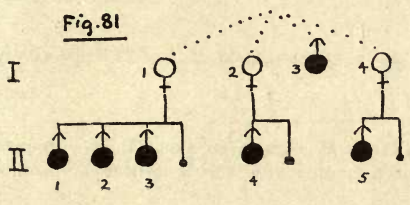
uncles. Parents normal. No recovery. II, 1 affected at 20; II, 2 at 13; II, 3 at 28; II, 4 at 13; II, 5 at 21; II, 6, sister, place in childship not

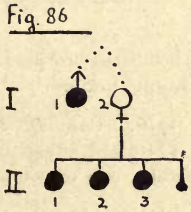
stated, escaped. I, 1 and 2, two brothers of mother affected, ages at onset not given.

1867 and 1871.* Case 80. Hutchinson, *R.L.O.H.*, vii, p. 170, and ix, p. 301, and *Med.-Chir. Trans.*, l, 1867, Case 24.

Mother, I, 2, affected at 43, her son and her nephew (II, 2 and 1) as young adults (exact ages not given). No note as to sex of I, 1 or siblings of II, 1 and 2.

1872 and 1873.* Case 81. Daguenet and Galezowski, *Journ. d'Ophthalmologie*, i, 342, and Prouff, *Thèse de doctorat*, No. 112, Paris.





I, 3 affected at 21; II, 1 affected at 26; II, 2 at 24; II, 3 at 21; II, 4 at 27; II, 5 at 21. The three mothers, I, 1, 2, 4, normal.

1873.* Case 82. Leber, *Nagel's Jahresbericht*, ii, p. 324, foot-note.

Two brothers; elder affected in twentieth year, R. beginning six months before L., no recovery; younger brother (age not stated) affected in exactly same way.

1874. Cases 83–85. Mooren, *loc. cit.*, p. 87.

Two brothers; *ibid.*, two other brothers; *ibid.*, three brothers. Ages of onset not given. One of them with V. reduced to J. 15 improved to reading J. 1 in eighteen months.

1874. Case 86. Alexander, *K.M.f.A.*, xii, p. 62.

I, 1 age of onset not given; did not recover. II, 1–3, sons of sister of I, 1. II, 1 affected at 29; II, 2 at 23; II, 3 at 20; all attacked in same year. No recovery. No other cases in family. (*Sex signs omitted in II, by oversight.*)

1876. Case 87. Pufahl, *Berliner klin. Wochenschrift*, No. 10.

I, 1 affected in his youth, and improved enough to read writing. II, 1 affected at 21; II, 2 at 27, "temporary improvement" in both; II, 3 affected, no particulars. The three sisters and parents normal.

1878. Case 88. Pufahl, *Beiträge z. prakt. Augenheilk. v. Hirschberg*, iii, p. 75.

I, 1 and 2 affected at 20; I, 3 not until 57; II, 1 at 19; II, 2 at 17. No improvement. Parents normal.

1879. Case 89. Fuchs, *K.M.f. A.*, xvii, p. 332.
In a childship of eight, first-born (♂) and four sisters normal. The

Fig. 87

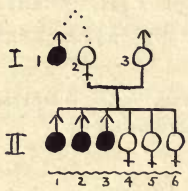


Fig. 88

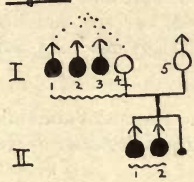
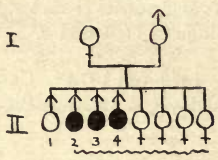


Fig. 89



other three brothers (II, 2, 3, and 4) affected at 32, 25, and 22 respectively. Parents normal.

1879.* Case 90. *Ibid.*
I, 1 and 2 affected at 21 ; I, 1, æt. 59 years when seen ; I, 3 to 6 normal sisters, one of whom (6) had five sons and one daughter by normal

Fig. 90

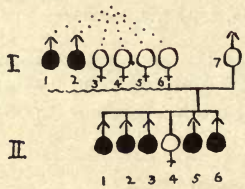
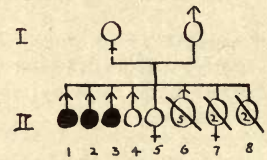


Fig. 92



husband. The five sons (II, 1, 2, 3, 5, 6) all affected, II, 3 at 33, the other four about 20–21. No recovery.

1879. Case 91. *Ibid.*
Three brothers; eldest affected at 52, next at 49, last at 48. No recovery.

1880.* Case 92. Higgens, *Med. Times and Gaz.*, i, p. 450.
Father, I, 2, died at 74, 1878, good sight, his last child then quite young. Mother, I, 1, living in 1880, good sight, had fourteen conceptions, of which two miscarried; five boys and two girls (II, 6 and 7) died young of measles or whooping-cough; five living at date of record, *viz.*, II, 1 affected at 16, II, 2 at 15, watched till 19, no recovery, severe case; II, 3, age at onset not given, but apparently younger than 1 and 2; II, 4 and 5 quite young at date of record.

1882.* Case 93. Norris, *T.A.O.S.*, iii, p. 355.
Five generations; transmission by affected males. No consanguinity. I, II, and III, 1, all said to have been affected. IV, 1 affected, but after

being "blind" recovered enough sight to resume ordinary occupations; his son (V, 1) affected, no details. IV, 2 normal, had nine children (V, 2–10), of whom first (V, 2) was affected at 48 and seen at 49, and fourth (V, 5) seen at 43, age at onset not given. The two daughters (V, 3 and 8) normal at 46 and 33 respectively. The other five died in infancy,

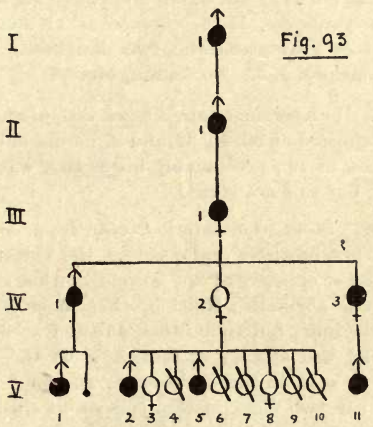


Fig. 93

sexes not stated. IV, 3 affected, age of onset not recorded; her son (V, 11) affected at 49, seen at 50. "Most became affected between 25 and 40."

1882. Case 94. Schlüter, "Über Neuritis Optica," *Inaugural Dissert.*, Bonn.

Family I. I, 1 and 2 normal sisters. II, 1 affected at 25; II, 4, 5, 6

Fig. 94

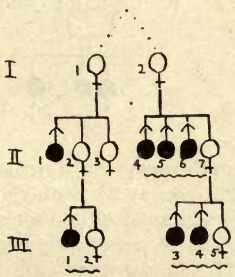
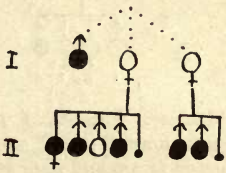


Fig. 95



all affected at 20. III, 1 at 20; III, 3 and 4 between 17 and 20 No consanguinity.

1882.* Case 95. *Ibid.* Family II.

I, 1 affected at 20; his two sisters, I, 2 and 3, normal. II, 1 affected

at 39, seen at 44; II, 2 affected at 12, seen at 33; II, 4 affected at 25, died at 28 of diabetes; II, 5 and 6, brothers, affected at 20. No consanguinity. No record of any sisters in II. (*Numerals omitted from Figure, in error.*)

1882.* Case 96. *Ibid.* Family III.

I, 1 affected at 20; I, 2, age at onset not stated; I, 3 normal. Of her four children the youngest, II, 4, affected at 11 and seen soon after; eldest, II, 1, æt. 24 years, and the two daughters, normal. I, 4 an affected female cousin of I, 3. No consanguinity.

1883. Case 97. De Keersmaecker, *Récueil d'Ophtal.*, 1883, p. 193.

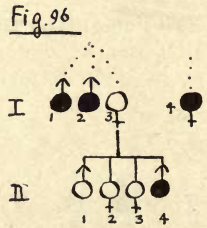
Four brothers affected at 20, 40, 32, and 37; order of birth not recorded. Also a male nephew at 19; presumably his mother was sister to the four affected brothers, but this not stated.

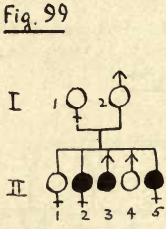
1885.* Case 98. Story, *Ophthalmic Review*, iv, p. 33.

In a sibship of 8, 4 brothers and 4 sisters, the eldest brother affected before 23, and died of epilepsy at 23; second brother affected at 21, died of phthisis, and was alcoholic; third brother affected as a young man, and died in an asylum; fourth brother affected at 30, was 45 at date of record, and had had attacks of insanity. Of the sisters, the third, affected at 40, was seen in the early stage at about same date as the fourth brother; her two older sisters (places in sibship not recorded) very excitable; youngest sister and eighth born normal.

1885.* Case 99. Holz, "Drei Fälle von genuiner Atrophia nervor. opticor. simplex progressiva bei Geschwistern," *Inaug. Dissert.*, Greifswald.

Notwithstanding the title the cases read like typical examples of





Leber's disease. Parents (I, 1 and 2) and grandparents normal; II, 1, æt. 28 years, normal; II, 2 affected at 22, seen at 23 (author's Case 3); II, 3 affected at 18, and seen at same age and until 20 (author's Case 1); II, 4, æt. 18 years, normal; II, 5, affected at 15, seen nearly a year later (author's Case 2). No improvement of II, 3 in two years.

1887.* Case 100. Habershon, *T.O.S.*, viii, p. 190. Author's Case 1.

Two brothers; one failed at 22 rapidly, seen at 31, had not improved; My. 1·5 D., V. J. 19; married at 19, and had two children before eyes failed, who are living and well. Other brother, five years younger, failed

at 17, seen at 26 (same time as elder brother), and again at 34 (1895); no improvement; V. J. 16, close to and fingers 2 m., My. 6 D. There are several other brothers all normal (no mention of sisters); parents saw well; father died of cancer, mother phthisis.

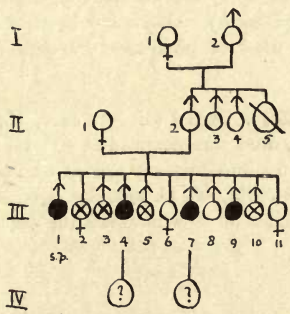
1887.* Case 101. *Ibid.*, Case 2 (E. N.'s case, P. 4, 215).

Three brothers: one affected at 31, and seen at 32; the other two failed in exactly same way, but ages not given.

1887.* Case 102. *Ibid.*, Case 3 (E. N.'s case, P. 14, 177).

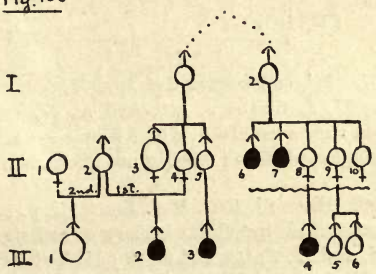
I, 1 a weakly woman; I, 2 died of cancer at 67; II, 1 not much information, but no cases known on her side; II, 2 was one of a very large sibship, of whom only three lived to grow up, all males; he died

Fig 102.



at 55; no consanguineous marriages; no recoveries; III, 1 affected at 16, seen at 45; married, no issue; III, 4 affected at 15, seen at 39, some children; III, 7 affected at 17, at 32 had some children; III, 9 affected at 12, æt. 27 years when III, 1 was 45; III, 2, 3 and 10 died of phthisis between 17 and 22; III, 5 of disease of spine at 24; III, 6, 8 and 11 (æt. 24 years) normal.

Fig. 103



1887.* Case 103. *Ibid.*, Case 4 (E. N.'s case, P. 10, 26).

I, 1 and 2 brothers, normal; II, 6 affected at 21, æt. 50 years at date

(1884); II, 7 not affected until 60, and became diabetic later; III, 2 affected at 34, no recovery, living aged 55 (1906); III, 3, age of onset not known; III, 4 affected at 16; II, 3 all died of phthisis, normal sight; II, 8, 9 and her two adult sons III, 5 and 6, and II, 10, single, all normal.

1887.* Case 104. *Ibid.*, Case 5 (E. N.'s case, *T.O.P.*, iii, p. 147, and *T.I.P.*, 1881, and pp. 5, 11 [Crane]).

Two brothers: the elder attacked at 22, and seen soon after; the younger attacked at $19\frac{1}{2}$, seen at intervals for four years, and V. remained about $\frac{6}{60}$. The brothers failed within about four months of each other. A brother of their mother (Boxall) has had bad sight many years.

1887.* Case 105. *Ibid.*, Case 6 (E. N.'s case, *M.*, i).

Two brothers and, perhaps, a sister. Elder brother affected at 23, æt. 30 years at record, no recovery; other affected brother failed at 19 when elder brother was 30. A sister bad sight and wears glasses, not seen, and has fits (? epileptic). One other brother and two other sisters normal; the brother died of phthisis. Parents normal sight; father died of phthisis.

1887.* Case 106. *Ibid.*, Case 7 (E. N.'s case, *M.*, i).

II, 1 attacked at 23, died unrecovered at 40; II, 2 married at 23, and had eight children and one miscarriage in eighteen years, the eldest æt. 17 years; the last child, æt. 11 months, born when she was 40; all suckled. Her sight failed at 40 when suckling last child.

Fig. 106

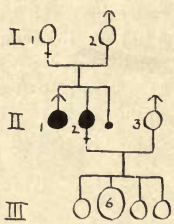
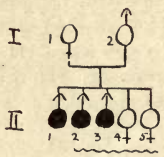


Fig. 107



1888.* Case 107. Edgar Browne, *ibid.*, p. 235.

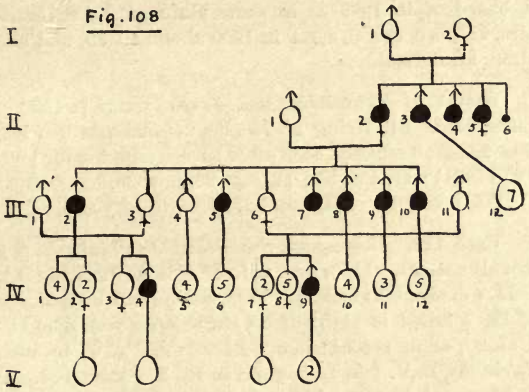
Three brothers; II, 1, firstborn, attacked at 27, seen at 40; II, 2 attacked at 32, seen very soon after; III, 3 seen soon after onset, age not given. The two sisters, places in sibship not given, normal.

1888.* Case 108. Haswell, *Brit. Med. Journ.*, ii, p. 1279.

I, 1 and 2 normal, but an indefinite history of bad sight in relations of I, 2. II, 1 normal, and II, 2 attacked at 48; II, 3 at 9; II, 4 at 21; II, 5 at 14. III, 2 attacked at 27; III, 5 at 33; III, 7 at about 20; III, 8 at 29; III, 9 at 18, æt. 37 years at record; III, 10 at 20. IV, 4, age at attack

not given; IV, 9 at 17. Four of those affected were seen; onset rapid in all, then stationary at V. about fingers, with atrophic discs when seen

Fig. 108



about 15 to 20 years after onset. In March, 1909, Dr. Haswell was unable to supplement the notes.

1888.* Case 109. Thomsen, *Münch. med. Wochenschr.*, xxxv, p. 222; *Berliner Gesellsch. f. Psychiatrie u. Nervenkrankheit* (1888).

Six brothers, and two of their maternal uncles. Age of onset 21 in one of the six brothers, not given for the others.

1892.* Case 110. Taylor (S. Johnson), *T.O.S.*, xii, p. 146, and later notes, 1909.

Pedigree of four generations: I, 1 became blind or nearly so at 40, eyes

Fig. 110

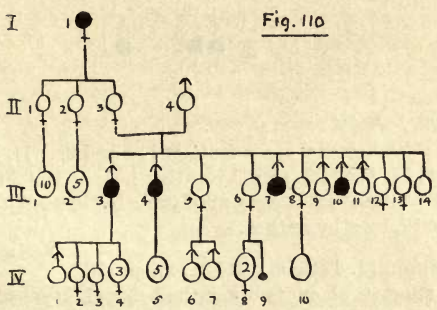
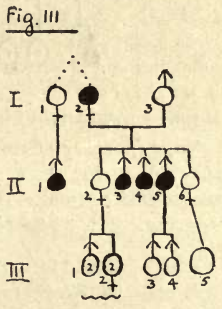


Fig. 111



looking natural. II, 1 and 2 had respectively 10 and 5 normal children. II, 3 married 4, both normal and not consanguineous; issue, 11 children, all grew up, and one miscarriage; of the 6 sons, 4 affected, III, 3 at 26, seen at 27, died of lung inflammation at 37, leaving one son (a soldier in

1909, with good sight), and 5 daughters, all good sight; III, 4 affected at 21, seen at 25, living in 1909 and has 5 normal children; III, 7, one eye only affected at 6, and still same in 1909; III, 10 affected at 6, seen at 13, and heard of in 1909 as in same state at 30, unmarried. The 3 daughters, III, 5, 6, and 8, aged in 1909 about 40, 39, and 35 years, have 19 children, all normal.

1891.* Case 111. Sym, *Edin. Med. Journ.*, xxxvi, p. 1133.

I, 2 affected at 51, living at 75; her ascendants not known. II, 1 affected at 26; II, 3 affected soon after severe cupping for yellow fever at 20, now 47 (1891); II, 4 at 33; II, 5 at 25, now 36, has two sons of 8 and 6 (1891) (III, 3 and 4). III, 1 and 2, æt. 18 to 12 years, all normal.

1892.* Case 112. Despagnet, *Soc. Franc. d'Ophtalmol.*, p. 392.

I, 1 to 4 all normal. II, 3, first wife of 4, issue normal; 1, 2, and 4 all normal; II, 4 died at 62, alcoholic; II, 5, second wife of 4, died at 58; of her siblings, II, 7 failed in sight at 50, cause unknown, died at 52. III, 3 affected at 26, 41 at record; her "eldest son," (IV, 1) affected at 20, papillitis chiefly L. V. ½ in L., normal in R., F. contracted. III, 4 at 30; III, 5 at 31, married at 27; III, 6 at 32, married at 28; III, 7 doubtful, slight case, at 30. No consanguinity. (*Cf.* Case 110.)

Fig. 112

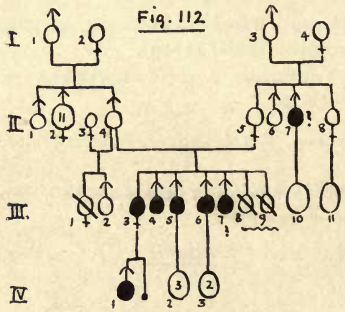
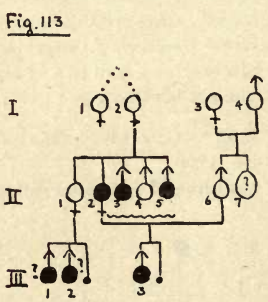


Fig. 113



1892.* Case 113. Somya, *K.M.f.A.*, xxx, p. 256.

Vague history of similar blindness in ascendants of I, 1 and 2. II, 2 affected at 34, II, 3 at 28, II, 5 at 18, seen by author; II, 6 and his ascendants normal. III, 1 "blind," III, 2 very amblyopic but exact data wanting. III, 3 affected at 19, seen by author.

1892.* Case 114. Thompson (J. Tatham), *T.O.S.*, xii, p. 156.

A man, æt. 37 years, R. affected about two months before L., typical, except for a small hæmorrhage in L. retina near O.D. in early stage when neuritic appearances were present. A brother of his mother was "blind" from "disease of optic nerves."

1896. Case 115. Ogilvie (F. Menteith), *T.O.S*, xvi, p. 3.

Three brothers in childship of 16; II, 4 affected at 24; II, 9 at 27; II,

13 at 22. Eight others died in infancy and 2 miscarried. III, 1 to 10, æt. from 6 years to a few months, the twins (III, 2) and III, 6 died or still-born. I, 6 and 7 normal; one of I, 5, and also II, 14, bad hysterical fits. In II, 9 L. eye improved from $\frac{3}{60}$ to $\frac{6}{24}$ in between two and three months.

1896.* Case 116. Batten (R. D.), *T.O.S.*, xvi, p. 125.

I, 1 and 2 and collaterals normal. II, 1 affected at 11, seen at 51, no

Fig. 115

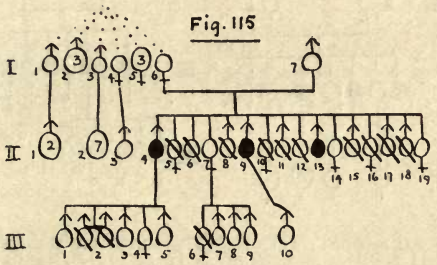
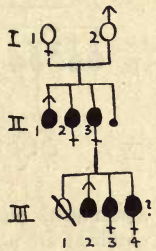


Fig. 116



improvement; II, 2 affected at 10, died at 33; II, 3 at 12, seen at 48 with V. $\frac{2}{60}$, age at marriage not stated; has had only 4 children, 3 of them affected; III, 1 died æt. 3 years; III, 2 affected at 11, V. with H. 4·5 D. corrected $\frac{6}{12}$, four months later $\frac{6}{24}$, a year after second note $\frac{6}{6}$; III, 3 failed down to $\frac{2}{60}$ at æt. 9 years, with pale O.Ds.; III, 4 failed at 8, with H. 3 and slight As. corrected $\frac{6}{9}$, O.Ds. much congested; two years later only $\frac{6}{12}$ (1898). No consanguinity.

1897.* Case 117. Snell, *T.O.S.*, xvii, p. 66. Author's Case 1.

I, 1 to 4, and II, 1 to 3 all known to have had good sight. In III, 1 æt. 32 years; 4, 29; 5, 27; 7, 24; and 8, 21, all severe amblyopia from their earliest recollection with pale O.Ds. and no other changes, no scotoma (but V. "better at night") and no contraction of Fs. V. from $\frac{3}{60}$ in III, 1 to $\frac{6}{24}$ in III, 8. III, 2 doubtful, is colour-blind like the rest, but V. R. $\frac{6}{6}$, L. $\frac{6}{12}$, and no note of condition of O.D. IV, 1 and 2, young children, 1 æt. 3 years examined and normal.

1897.* Case 118. *Ibid.* Author's Case 2.

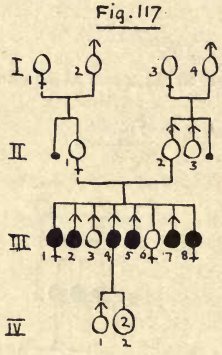
Two brothers, both affected in same way at 17 years. No consanguinity and no other cases known in relations.

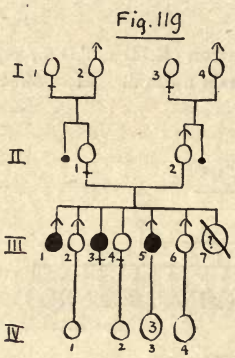
1897.* Case 119. *Ibid.* Author's Case 5.

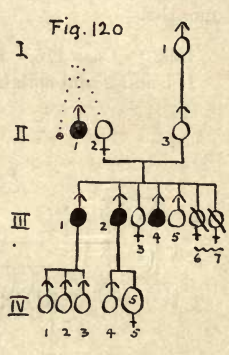
III, 1, 3 and 5 all affected at 13, seen at same date at 40, 32, and 26 respectively. III, 2 at 36; 4 at 29; 6 at 23, normal. III, 1 and 3 married some years, no issue; III, 5 has three normal children. All in I and II lived to good age with good sight. No consanguinity. II, 1, 63, and 2, 64 at record, and were about 22 and 23 at marriage.

1897.* Case 120. *Ibid.* Author's Case 6.

II, 1 "blind" in middle age and never recovered; II, 2 lived to 85, good sight; II, 3 lived to 67, he and I, 1 good sight; III, 1 affected at 52, seen





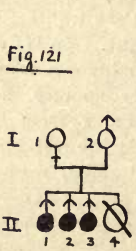


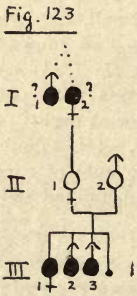
again at 62, has three sons all normal; III, 2 at 57, seen same time, six children all normal, subject to fits from age of 24 to 40; III, 4 affected at 36, seen at 44, married, no issue. III, 5, æt. 43 years; III, 6 and 7 died in infancy. No consanguinity.

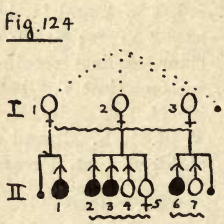
1896. Case 121. Velhagen, *Deutsche med. Woch.*, p. 841.

Three brothers affected, II, 1 at 19, II, 2 at 25, II, 3 at 20, æt. 24 years at record; several others died young. Parents normal.

1897.* Case 122. Higier, *Deutsche Zeitschrift f. Nervenheilkunde*, x, p. 489.







I, 1 affected at 20, and improved in about a year. II, 1 at 27, seen soon after; II, 2, six years younger than II, 1, affected at 20; II, 3 epileptic and subject to migraine. Parents normal and not consanguineous.

1900. Case 123. (First of Leber's 9 new unpublished cases) Hormuth's text, p. 16, and his Tables, p. 114.

III, 1 affected between 22 and 23, nine months' interval between the two eyes, final result not reached at date of record; III, 2, L. six months before R. at 22; R. recovered perfectly, L. did not recover seen finally five years after onset; III, 3 affected at 17, improved somewhat, but not enough to read; I, 2 was "blind" for six months at 27, but recovered; her brother, I, 1, also had some disease of the eyes, and got better.

1900.* Case 124. *Ibid.*, p. 11. Family 1. Tables, p. 110.
Four males, sons of three sisters, ages not given; first case (II, 1) seen a year after onset.

1900.* Case 125. *Ibid.*, p. 12. Family 2. Tables, p. 110.
Two brothers; elder affected at 39, younger at 18. Family history not given.

1900.* Case 126. *Ibid.*, p. 14. Family 3. Tables, p. 112.
Two brothers affected at 20 and 27; an uncle, brother of their mother, had same disease at 24.

1900.* Case 127. *Ibid.*, p. 18. Family 5. Tables, p. 116.
Two male cousins affected at 21 and 30; their mothers were sisters. A brother of the two mothers, maternal uncle of the other two cases, also affected at about 18 or 20.

1900.* Case 128. *Ibid.*, p. 20. Family 6. Tables, p. 116.
In a childship of 5, the 2 brothers affected at 25 and 17, and of the 3 sisters, 1, much younger than the brothers, affected at 42; the other 2 sisters normal. Parents normal.

1900.* Case 129. *Ibid.*, p. 20. Family 7. Tables, p. 118.
Two brothers, affected at 24 and 32. History incomplete.

1900.* Case 130. *Ibid.*, p. 22. Family 8. Tables, p. 118.
In a sibship of 8, 2 brothers affected at or about 20; the elder now 40, the other quite recent, æt. 20 years, at date of record. Parents normal.

1900. Case 131. *Ibid.*, p. 23. Family 9. Tables, p. 118.
Two brothers affected at 18. Nothing else recorded.

1900.* Case 132. *Ibid.*, p. 154. Leber's supplementary cases, not previously published, given to Hormuth. Family 1. Not in tables.
Sibship of 3; 2 brothers, the elder affected at 27, the other, 9 years younger, at 18; one sister between them normal. Both recovered, the elder to being able to read, the other to being able to resume his painting.

1900.* Case 133. *Ibid.*, p. 157. Family 3. Not in tables.
I, 3 affected, but age of onset not noted. II, 1 and 2 each affected at about 23, 1 being two years older than 2. One normal sister, age not given.

1900.* Case 134. *Ibid.*, p. 156. Family 2. Not in tables.

Two brothers; one affected at 14, seen at 40, V. $\frac{20}{100}$ or $\frac{20}{200}$; the other about two years younger, not affected till 40, seen soon after. No other cases known in family.

1900.* Case 135. *Ibid.*, p. 158. Family 4. Not in tables.

Nephew and uncle; nephew attacked at 31 and seen at 37; age of onset in mother's brother not recorded.

Fig. 133

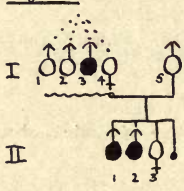


Fig. 136

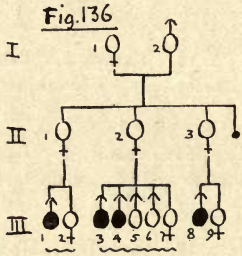
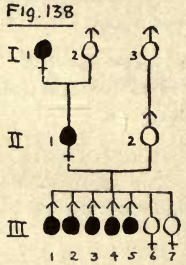


Fig. 138



1900.* Case 136. *Ibid.*, p. 158. Family 5. Not in tables.

I, 1 and her husband, 2, a physician, normal. II, 1, 2, 3, three normal daughters; no record of any other children. III, 1 affected at about 55, seen some months later, and improved definitely in four months; III, 3 affected at 22; III, 8 at 40; age at onset in III, 4 not given.

1900.* Case 137. *Ibid.*, p. 160. Family 6. Not in tables.

Two brothers; one failed at about 48, seen two and a half years later, æt. 51 years; other brother affected at 27, present age not given. Parents, good eyes.

1899.* Case 138. Strzminski, *Ann. d'Oculistique*, cxxi, p. 99.

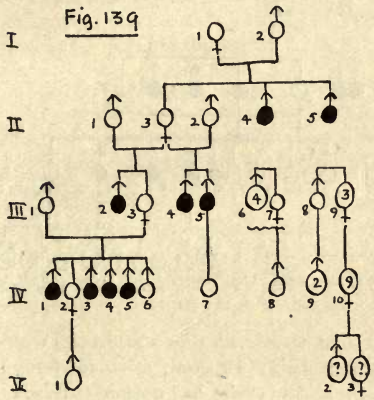
I, 1 said to have had the disease. II, 1 affected at 25, seen at 58 (1897), typical central defect with also concentric contraction of Fs. III, 1 affected at 24, seen at 36 (1897); III, 2 at 25, seen at 35. Age of onset in III, 3, 4, and 5 not given. One of these three epileptic, and others mentally affected.

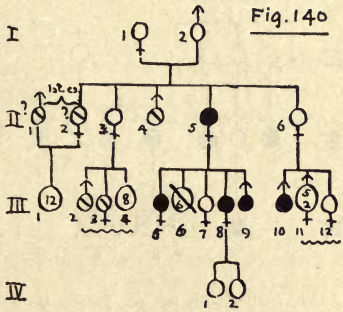
1895.* Case 139. Westhoff, *C.f.A.*, p. 168.

Five generations. I, 1 and 2 normal, had one normal daughter, II, 3, who transmitted the disease to her sons by both her husbands, and 2 sons, II, 4 affected at 25, and II, 5 at 23; all their descendants in III and 4 and 5 to date, normal. III, 2 affected at 20; III, 4 and 5 both at 19. IV, 1 at 21; IV, 3 at 22; IV, 4 at 17; IV, 5 at 19. *Connecting line between II, 4 and his children III, 6 and 7, also between II, 5 and his children III, 8 and 9, accidentally omitted in the Figure.*

1895. Case 140. E. N., unpublished, St. Thomas's Hospital, 1890–91. (Pitt, Barrett, and Wilson.)

I, 1 and 2, no information. II, 2 to 6, their issue. II, 2 had bad sight and married a first cousin with bad sight, but no particulars of the disease or of kind of cousinship, nor of sight of their 12 children (III, 1). II, 3 had 10 children, of whom a son and daughter (III, 2 and 3) had some defect of sight, but no details. II, 4 also some unknown affection





of sight; II, 5 affected at 14, and went to Moorfields then; living, æt. 61, in 1891, sight not improved; II, 6 living, with good sight. III, 5 (Mrs. Pitt) failed at 36, married at 18, no children; III, 8 (Mrs. Barrett) failed at 26, has had children, too young to show the disease (IV, 1 and 2); III, 9 (Lynham) failed at about 22, seen nine months later; III, 10 (Wilson) failed at 22½ after influenza, seen six months later; III, 12 (fifth born), fits.

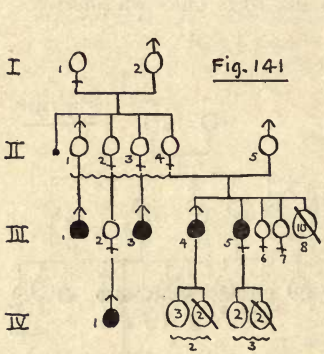
1895. Case 141. E. N., unpublished, St. Thomas's Hospital, 1885 and 1893. (Donovan.)

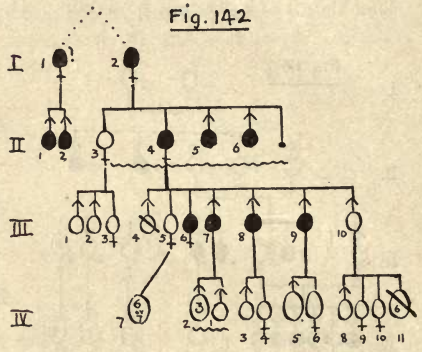
I, 1 and 2 had good eyes. II, 1, Hodgkins, of Birmingham, had a son (III, 1) affected at about 40; II, 3 married Jones and had son (III, 3) affected so early that he never learned to read, æt. 30 years in 1893; II, 4 married Donovan II, 5 and had issue. III, 4 (J. Donovan) affected at 30, seen at 36 and again at 43; III, 5 (Mrs. Leonard) married at 22, affected at 33, and seen soon after; III, 8, 10 who died quite young. IV, 1 affected in early life, could never see his work properly; IV, 2, five children of III, 4, two dying early; IV, 3, four children of III, 5, two dying early.

1895. Case 142. E. N., unpublished, Moorfields Hospital, 1896. (Laxford.)

I, 1 believed to have had bad sight; had two sons undoubtedly affected like the rest (II, 1 and 2); I, 2 certainly affected; had one normal daughter (II, 3) with normal children (III, 1, 2, and 3), one affected daughter (II, 4) and two affected sons (II, 5 and 6); no record of other

children. II, 5 and 6 apparently s.p., but II, 4 had seven children, *viz.*, III, 4 died in infancy; III, 5 died unaffected at 60, probably heart failure; III, 6, æt. 60 years in 1896, no issue, believed to be affected;

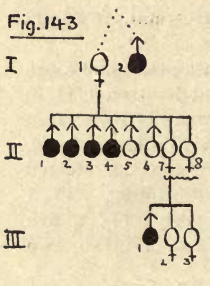


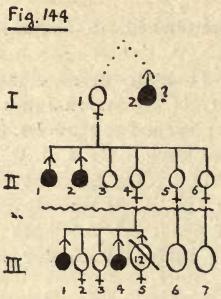


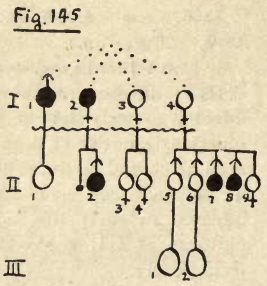
III, 7 affected, æt. 58 years in 1896, had then had four children, IV, 1 died of influenza, and 3 living; III, 8 probably affected, died suddenly at 30; III, 9, patient, failed at 26, seen at 56 (1896), has normal children (IV, 5 and 6). IV, 8 to 11, 9 children of III, 10, 6 of whom died young.

1895. Case 143. E. N. (unpublished), Moorfields Hospital, 1897. (Philbrick.)

I, 2 was affected; II, 1 affected at 14, recovered sufficiently to be able to read; II, 2 affected at 33; II, 3 and 4 each at 25; II, 5 and 6 are the last born of the childship; III, 1 patient, æt. 22 years.







1895. Case 144. E. N. (unpublished), Moorfields Hospital, 1890. (Haile and Drudge.)

I, 2 reported to have had the family blindness; II, 1 to 6, order of birth not known; II, 1 and 2 affected; II, 4 had 16 children, of whom first born, III, 1, was affected at 22 and seen at 29, unmarried; III, 2 and

3 unmarried; III, 4 affected at 17, and seen then; III, 5, 12 who died young. No consanguinity.

1895. Case 145. E. N. (unpublished), Moorfields Hospital, 1891. (Booty.)

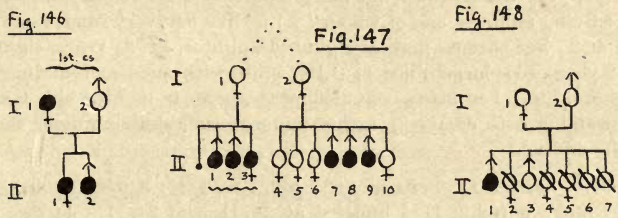
I, 1 affected, "nearly blind," has children, but no details; I, 2 similarly affected, and has an affected son (II, 2); II, 7 affected at 12, seen at 49, no recovery, married, no issue; II, 8 also affected, unmarried; II, 9 unmarried. No consanguinity.

1907.* Case 146. Gunn (R. Marcus), *T.O.S.*, xxvii, p. 221.

Incomplete, and cannot be completed. I, 1 affected in childhood, married a first cousin (kind of cousinship not recorded), and had (up to 1907) two children; II, 1 affected at 5, seen at 8; II, 2 affected at 3, seen at 4.

1887.* Case 147. Lawford, *St. Thomas's Hospital Reports*, xvii, p. 158. Author's Case 1.

I, 1 and 2 sisters; I, 1 had at least three children, of whom II, 1 certainly got the affection at 19, and 2 and 3 probably suffered; I, 2 had



seven children, of whom all the sons suffered; II, 7 at 31, seen at 32; II, 8 (4 years younger than 7) at about 18; and II, 9 (3 years younger than 8) at 19; eldest, II, 4, æt. 39 years, and youngest, II, 10, 22 at record; II, 7 was also congenitally colour-blind.

1887.* Case 148. *Ibid.* Author's Case 2.

I, 1 good sight, but epileptic fits, husband good sight; II, 1 affected at 18; II, 3 living and normal; II, 2 died at 2, "consumptive bowels"; II, 4 still-born; II, 5 at 1 year; II, 6 and 7 at 1 year of diarrhœa.

1875.* Case 149. Schilling, *Inaug. Dissert.*, Berlin.

I, 2 married twice, by first husband (I, 1) three sons; II, 1 affected at 14, seen at 38; II, 2 affected at 10½, seen at 36; II, 3 began at 29, seen at 34; by second husband (I, 3) 2 sons; II, 4 affected in eleventh year, 26 at record; II, 5 affected in twentieth year, 24 at record; one daughter II, 6, who at 20 became extremely amblyopic of both eyes (fingers 12 in.) with contracted Fs. but no ophthalmoscopic changes, and recovered perfectly; no note about her pupillary reaction; probably hysterical amblyopia. No positive information about vision in parents, nor as to consanguinity.

1890. Case 150. Nicolai, *Nagel's Jahresbericht*, xxi, p. 353. (Original in Dutch, not seen.)

Three brothers attacked at 32, 29 and 25, and a nephew at 36; no female suffered.

Fig. 149

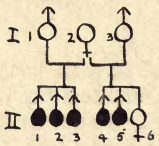


Fig. 152

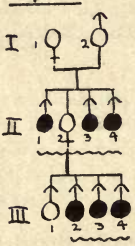
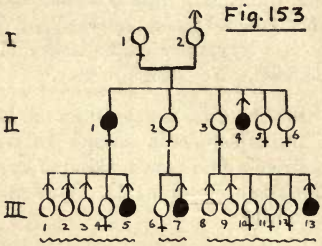


Fig. 153



1895.* Case 151. Linde (Max), *C.f.A.*, p. 363.

Mother and daughter. Mother, æt. 26 years, sight bad as now from earliest recollection; fingers 8 feet, scotoma, O.Ds. white, retinal vessels normal; very undergrown, but well-proportioned, teeth and skull normal; has 4 living siblings, one of whom (♀) is, like her, very small; one other died at 2; her parents normal sight. Daughter, æt. 3½ years, sight failing 2 years, sees large objects; O.Ds. white with some surrounding haze, no choroiditis; had many convulsions at about 18 months old; teething and walking both delayed; rather undergrown; skull normal; no note of any siblings.

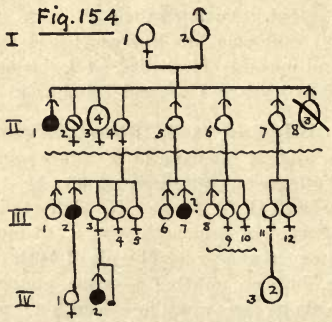
1897.* Case 152. Leitner, *Szemészet*, Nos. 3, 4. Author's Case 1.

I, 1 and 2 normal; II, 1 affected at 23, II, 3 at 24, II, 4 at 25; III, 1 normal, III, 2 affected at 25, III, 3 at 23, III, 4 at 24.

1897.* Case 153. *Ibid.* Author's Case 2.

I, 1 and 2 both normal: II, 1 affected at 39, II, 4 at 25, III, 5 at 13, III, 7 at 22, III, 13 at 20.

Fig. 154



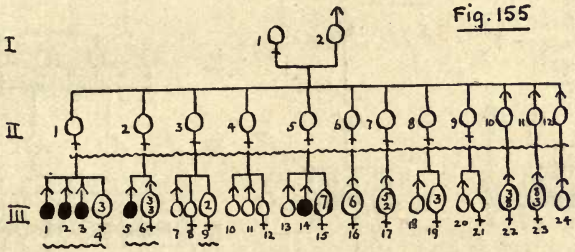
1898.* Case 154. Posey, *Ann. of Ophthal. and Otol.*, vii, p. 357.

I, 1 died at 60 and I, 2 at 72, both with good V. II, 1 (author's Case 3)

failed at 30. II, 2 had glaucoma, married, no issue. II, 8, 3 who died "young" but with good sight. III, 2 (author's Case 2) failed at 24, has one child of 14 (IV, 1). III, 7 "bad sight" without further details. IV, 2 (Author's Case 1) failed at 25; IV, 3 two young children, good sight. Married, but without issue, II, 3; III, 1, 4, 5, 9, 10, and 12.

1898.* Case 155. Leitner, second paper. *Ibid.*, No. 3. Author's Case 1.

I, both normal; II, 9 sisters and 3 brothers all normal and all having



children. III, 1 affected at 18, III, 2 at 24, III, 3 at 20; III, 4, three normal sisters; III, 15 at 18, æt. 24 years at record. III, 14 normal at 32; III, 24, 11 siblings, eldest 21; III, 25, another 11, eldest 24; III, 26 æt. 9 years. No consanguinity, no early deaths.

1898.* Case 156. *Ibid.* Author's Case 2.

I, 1, 2, and 3, normal. II, 1, æt. 20 years, and 2, æt. 18 years, also 3 and 4, all normal. II, 5 affected at 15, II, 6 at 12, both seen four years later, no recovery. No consanguinity.

1898.* Case 157. *Ibid.* Author's Case 3.

Single case in a ♂ coming on at 16, seen at 17; V., fingers 0·5m., symptoms typical; has 2 sisters, normal. No other details. No consanguinity.

1899.* Case 158. Magers, *Inaug. Dissert.*, Jena. Author's Case 1.

Male twins; one affected about a year before other, at about 16 and 17 respectively. R. eye failed before L. in both. Parents, good sight, but a brother of the mother had the same disease at about 20.

1901.* Case 159. Gallemaerts, *Policlinique*, Bruxelles, April 1st. Author's Cases 3 and 4.

I, 3 reported affected like the others, and all his 5 children (II, 6) said to have bad sight of the same kind; II, 1 affected at 21, æt. 33 years and unmarried at record (author's Case 4); II, 2 affected at 17, seen soon after (author's Case 3).

1901.* Case 160. Stood (Dr. W., of Barmen), *K.M.f.A.*, 39, i, p. 238.

Fourteen members of a family affected. Two of them, a young man whose case at first looked hopeless, and his sister, recovered V. $\frac{5}{6}$.

1902.* Case 161. Velhagen, *Münch. med. Woch.*, p. 941.

I, 1 died insane. III, 3 affected at 21, now 50 (1902). IV, 1 affected at 21, now 27; IV, 2 and 3, both at 21, now 44 and 29 with V. from $\frac{5}{30}$ to $\frac{5}{10}$. Numerous other descendants of I, 1, but no other cases. No known consanguinity.

Fig. 159

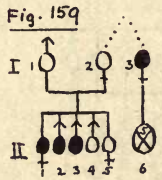


Fig. 161

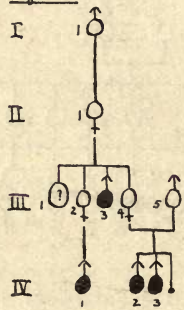
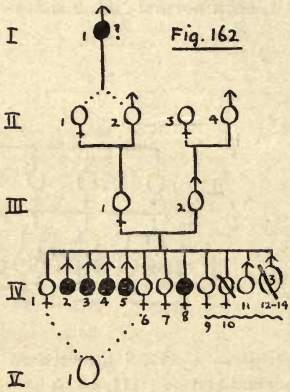


Fig. 162



1902.* Case 162. Lauber, *Wiener klin. Woch.*, p. 1264.

I, 1, father of either II, 1 or II, 2, was "blind"; no details. II, 1 to 4 all saw well to end of life; III, 1 died at 53 of liver disease; III, 2 lived to 73, good sight. IV, 1, probably firstborn, about 44 (1902), IV, 6, 37 and IV, 7, 36; two of these three sisters have several children, the eldest 12. IV, 2 affected at 22, now 43 (1902); IV, 3 at 22, now 42; IV, 4 at 27; IV, 5 at 22; IV, 8, patient, at 30, seen soon after, final result not known. None of the four affected brothers recovered; IV, 9 died at 13, IV, 11 at 11, IV, 10 at $1\frac{3}{12}$; the other three at a few months.

1902.* Case 163. Heinsberger, *Inaug. Dissert.*, Giessen. Author's Case 1.

I and II all said to have been normal; III, 1 affected at 20, 29 at record; III, 3 at 20, 24 at record; III, 5 at 20, seen soon after; skull normal.

1902.* Case 164. *Ibid.* Author's Case 2.

I, 1 and 2 affected at 20, one of them died of "cardiac dropsy"; I, 3 also died of "dropsy" at 60; I, 4 at 70 of "stroke"; II, 1 said to have had "weak sight"; II, 2 affected at 21, no recovery, 47 at record; skull normal; II, 3, patient, at about 27, no recovery, 41 at record.

1906.* Case 165. Kowalewski, *C.f.A.*, xxx, p. 114.

I, 1 affected when in Army 1871, now about 55 (1905), no recovery.

II, 1 affected at 20, died of dropsy at 32 (1889), would be 48 in 1905, no recovery; II, 2 affected at 25, seen at 35 (1905), no recovery, married

Fig. 163

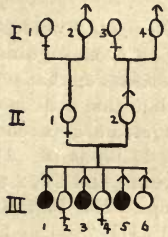


Fig. 164

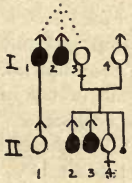
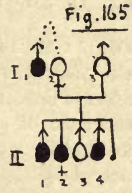


Fig. 165



at 28, no issue; II, 4 affected at 21 (1905), seen soon after, skull unsymmetrical, slight proptosis on both sides from shallowness of orbits.

1898.* Case 166. Raymond (F.), *Leçons sur la Maladies du Système Nerveux.* Troisieme série (Année, 1896–97), Paris, 1898, p. 399. Author's Family 1.

I, 1 and 2, first cousins, but kind of cousinship not given. II, 1 died of diabetes at 43; II, 2 living, 86 at record; II, 3 became rapidly blind at 30, probably optic atrophy, died at 49. III, 1 died at 43, cerebral tumour; III, 3 at 51, cerebral softening; they had a son, IV, 4 (author's

Fig. 166

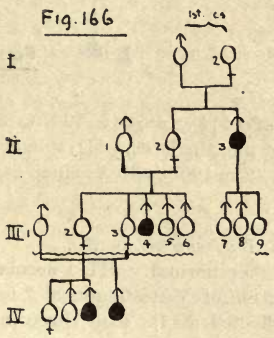
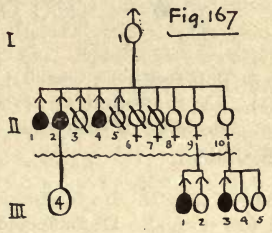


Fig. 167



Case 2), affected by typical Leber's disease at 26, seen at 38, no recovery; syphilis two years before failure of V. III, 4 affected at 24, seen at 53, said to have remained the same for 20 years, and then improved to reading largish letters; for years could only with difficulty see to go about (author's Case 3). IV, 3 affected at 22, seen at 26, somewhat improved, V. $\frac{1}{3}$ at record (author's Case 1). (*Indicating numerals to IV omitted in error.*)

1898.* Case 167. *Ibid.* Author's Family 2.

I, 1 gouty. III, 3 affected at 24, seen soon after (author's Case 4); III, 1 affected at 23, seen at 46, when he was absolutely blind and had paralysis agitans (author's Case 5). II, 1, 2, and 4, all suffered from same disease at almost same age as the other two. II, 3, 5, 6, died young; II, 7 died at 18.

1907.* Case 168. Coste, *Thèse pour le doctorat en Médicine*, Toulouse.

Four cases with typical symptoms and mode of descent; consanguinity of paternal ancestors of one case, but no cases of the disease on that side. Narrow base of skull in some of the affected ones, but this still more marked in III, 2 from unaffected division. No miscarriages, and apparently no early deaths. Ages in IV: 1 was 27 in 1907, 3 was 17, 6 was 16. III, 6 married at 19; only two children, IV, 1 born five years, and IV, 2 ten years after marriage; both labours natural, no forceps. III, 4 affected at 23, 58 at record (1907), unmarried (author's Case 2); III, 7 affected at

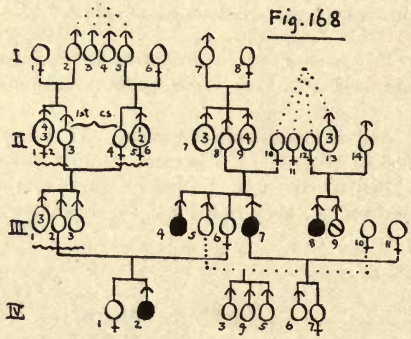


Fig. 168

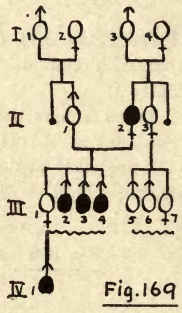


Fig. 169

35, 48 in 1907 (author's Case 3); III, 8 affected at 48, 53 in 1907 (author's Case 4). IV, 2 affected at $2\frac{1}{2}$, seen six months later. III, 9 had gross central choroiditis in both when seen at 42 in 1907, with V. much reduced and My. 2 D.

1909.* Case 169. Bach, *München med. Wochenschr.*, p. 210.

I, 1 to 4 normal. II, 2 affected, her sister normal. III, 1 normal, her three brothers affected, two with reduction of V. to fingers at 2 m., the other to V. $\frac{6}{18}$ in R., $\frac{6}{6}$ in L. IV, 1 affected at 15, seen three months after.

1909.* Case 170. Mr. Rayner D. Batten, *T.O.S.*, February 11th, 1909.

Single case in boy coming on at 8 in September, 1908, with slight neuritic appearances. V. went down to R. $\frac{6}{60}$, L. $\frac{6}{36}$, with Fs. much reduced, then, at end of December, began to improve rapidly, and by end of January, 1909, V. was $\frac{6}{6}$ in each, R. better than L. No other cases known, but mother very ignorant of the family history.

1909.* Case 171. *Ibid.*, *T.O.S.*, February 11th, 1909.

I, 1 affected. II, 3 affected. III, 1 affected at about 20, patient of Mr. Doyne at Oxford, now æt. 33 years, his six siblings all normal; III, 9 affected at 16, seen 1907 and again 1909 when æt. 24 years, V. $\frac{6}{60}$; III, 13 affected at 10 (March, 1904), V. down to $\frac{6}{60}$, in July began to improve, and by March, 1905, had recovered to $\frac{6}{6}$ each eye, and remained same in February, 1909 (æt. 15 years); O.D.'s became somewhat pale some months after onset. III, 12 died æt. 3 years; III, 14 also died in childhood. No miscarriages. III, 8 æt. 27 years. II, 9 died at 21; II, 10 married, no issue; II, 1 died at 40.

Fig. 171

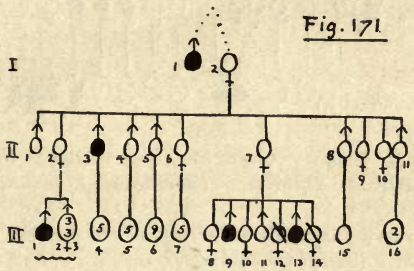
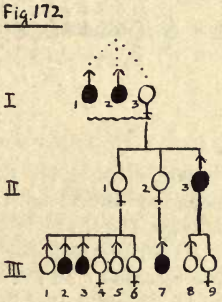


Fig. 172



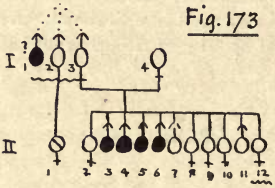
Case 172 seen by Leber, 1871; Magers, 1898; Vossius,* 1899–90.

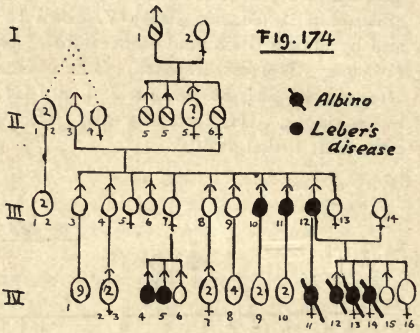
I, 1 affected at 20, no recovery, lived to 72; I, 2 at 21, no recovery, lived to 73; I, 3 normal, lived to 86. II, 3 affected in 17th year in 1866, and seen by v. Graefe then and by Ewers in 1869; married later and in 1899 had two sons and two daughters (*erroneously marked as one of each*), aged from 24 to 16 years. III, 2 affected at 23 (1894), improved, and in 1897 could read newspaper with a magnifier; had variola, whooping-cough, scarlet fever, and diphtheria in childhood, with nephritis and dropsy, and later paralysis of right arm and leg, and later of left leg, then good health till 16, when he had pneumonia, now (1897, æt. 28 years) healthy. III, 3 affected at 22, æt. 27 in 1897; III, 1 æt. 29 years, and III, 6 æt. 22 years (1897); III, 7 affected at 19, when he was seen by Magers two years later (1898) with V. fingers 5 m.

1896–1909. Case 173. Family of French. Messrs. Rayner D. Batten, Lawford, Worth, and E. N.

I, 1 failed in sight after a slight accident, and did not recover; I, 3 and 4 living, but no record of their sight, presumably both normal. II, 1 a blind and idiotic daughter of I, 2; she cannot walk. II, 2 to 12, 11 siblings, of whom 2 died at 5, the other ten living and aged (in 1909) from 41 to 20 years. II, 3 affected at 27 (1896, Moorfields, under care of E. N., seen by Mr. Batten, 1909); no recovery. II, 4 affected at about 37, attending Mr. Worth (Moorfields). II, 5 affected at about 22–23, now 36, and still attending Mr. Batten (Western Ophthalmic Hospital). II,

6 affected at 22 (1897), and still under Mr. Batten's care, æt. 34 years. Question of lead poisoning was raised, as at least three of the affected brothers were plumbers, but there was no decided evidence of plumbism.



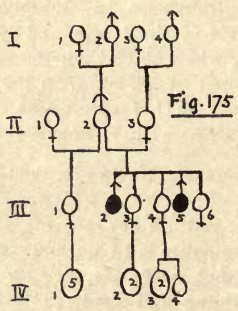


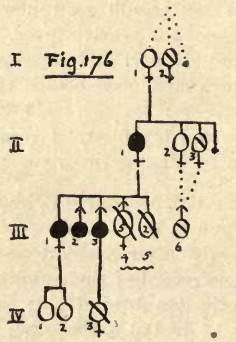
1906. Case 174. Mr. C. H. Usher. Cases of Leber's disease in a pedigree drawn up to illustrate albinism. (Forthcoming *Albinism Memoir*, Fig. 130.)

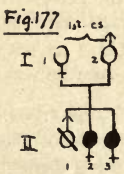
III, 10 and 11 Leber's disease set in at about 30; age of onset in III, 12 not recorded. In IV, 4 Leber's disease present at 30, and in IV, 5 at 25. In II, 6 sight failed in old age, and also in two of her brothers, but the nature of the failure not known. I, 1 also said to have failed in sight as an old man. The albinos were offspring of two mothers by same father, the father (III, 12) having Leber's disease, the two mothers almost certainly unrelated to each other. No consanguinity.

1899.* Case 175. Buisson, *Thèse*, No. 564. Paris, 1899.

I, 2 good sight at 86; no information about 1, 3 and 4; II, 1 first wife







of II, 2 had only one child (III, 1), who in her turn had five normal children (IV, 1); II, 3, second wife of II, 2, had five children (III, 2 to 6), of whom III, 2 failed at 30 and was seen at 31 (author's Case 2); and

III, 5 failed at 19, and was seen three months later (author's Case 1); IV, 1, 2 and 3 all normal, and no miscarriages or early deaths; IV, 4, a seven months child, paralysis of lower limbs.

1899.* Case 176. *Ibid.* Author's Cases 3 and 4.

I, 1 died of phthisis at 35; I, 2 died blind and paralysed at 50, no details of the blindness; II, 1 progressive failure of V. at 48 and optic atrophy found, at 50 sudden hemiplegia; II, 3 died from heart disease, blind, at 58, no details of the blindness; either she or another sister (II, 2) had a son (III, 6) who went "blind" at 30, no details; III, 1 affected at 31, seen at 33, no recovery (author's Case 4), has 2 children æt. 8 and 7 years (IV, 1 and 2), and no miscarriages; III, 2 affected during military service and recovered; III, 3 affected at 27, seen soon after (author's Case 3), has one child who died young; III, 4, five who died young; III, 5, two stillborn.

1866.* Case 177. Hutchinson, *R.L.O.H.*, v, p. 349.

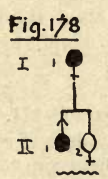
I, 1 and 2 first cousins, but kind of cousinship not noted; II, 1 died at 4 months; II, 2 said to have never seen, at 4 could only see large objects and O.Ds. very atrophied (author's Case 2); III, 3 thought to have seen well till 6 months old; at 1½ years sees large objects, O.Ds. very white. Both children intelligent and good tempered. Syphilis not mentioned. No other history of blindness in family. This case has sometimes been quoted as perhaps being an instance of Leber's congenital *retinal* atrophy without pigmentation.

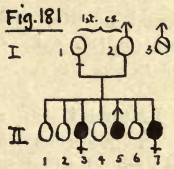
1907.* Case 178. Lawson (Arnold), *T.O.S.*, xxvii, p. 169.

I, 1 affected at 14, if not earlier; L. much worse than R., typical scotoma in each; now 31 (1907). II, 1 now 10 with typical scotoma in each, affected since early infancy. II, 2 age not stated, sees quite well. At date of record there had been no more births.

1903.* Case 179. E. N., *T.O.S.*, xxiii, p. 108.

Male affected in 28th year, perfect recovery in a year or year and a





half. His brother, ten years younger, attacked at 25; final result not known. Two males, first cousins, had the disease at æt. 28 and 35 years respectively; the latter is said to have recovered perfectly, the former did not. These two pairs of brothers were sons of two sisters.

1894. Case 180. König (Hormuth, p. 94).

Man, æt. 22 years, no recovery in one year. A brother of his mother (maternal uncle) and a cousin also on mother' side were blind of optic

atrophy; the uncle improved. Also a great uncle on mother's side was affected. Four cases, all males.

Case 181. E. N. (Littlechild). St. Thomas's Hospital (*Out-Patient's Book*, v, p. 133), February to May, 1890.

Blindness from birth with optic neuritis and large skull in three siblings. Probably not a true case of Leber's disease. Parents, first cousins, had 8 children and no miscarriages.

No history of blindness in rest of family, except, perhaps, in a male, "second cousin" of I, 3 said to have been blind all his life. I, 1 and 2 good health. No history of syphilis.

II, 1 and 2 good sight and health; one of them squints; 6 and *the next born, which by mistake is not shown and should be* 7, also healthy and see well. II, 4 died at 7 weeks, but could see.

II, 3, quite blind from birth; taken to Middlesex Hospital when a baby and told "the nerve was inflamed." February 28th, 1890, æt. 7 years; Ps. motionless before mydriatic, but dilate widely after its use; L. O. D. seen with difficulty; it is hazy, and one vein decidedly enlarged, but no swelling and no visible atrophy; R. not seen; shadows some H., but degree not measured. Cranium rather large, forehead broad and prominent, the eyebrows overhanging the orbits very much, so that the eyes are extremely sunken and look small, although really of normal size; nose short; face well formed; speaks well, and seems intelligent.

II, 5 was blind from birth; died at 15 months of age; no particulars.

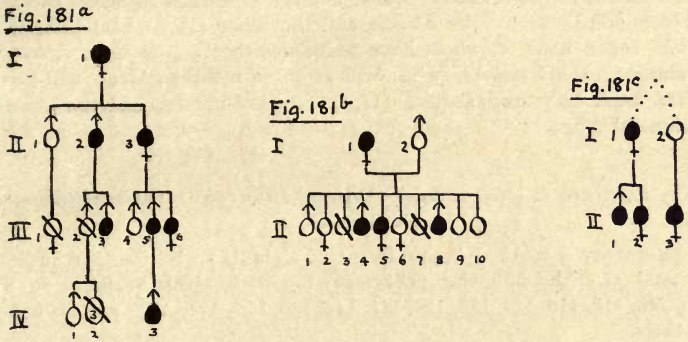
II, 8 (*erroneously marked* 7) brought in February, 1890, æt. 7 months. Appeared to have no p.l., and mother said she was certain the child had never seen. Her seeing children had all noticed the light very soon after birth; this one never did so at all. February 28th, 1890: Pupils small, equal and motionless to light; irregular slow nystagmic movements and frequent strong convergence of eyes. O.Ds. swollen and very hazy, and veins tortuous. Head large and square, fontanelle open, frontal eminences square; ribs slightly beaded; spleen $1\frac{1}{2}$ in. below costal margin; for some weeks past head sweating; suckled, but for the last two months some bread and oatmeal in addition; has had no illness and no fits. Though quite blind the child screws up her eyes in sunlight, but takes no notice of lamplight. Last seen in May, 1890, *in statu quo*.

Case 181*a*.* Rampoldi, *Ann. di Ott.*, xii, pp. 269–271.

I, 1 blind of "gutta serena" at 35, dead at date of record; II, 1 good sight; II, 2 became blind at 35 and II, 3 between 35 and 40, also of "gutta serena"; III, 3, optic atrophy came on in R., soon followed by L. early in 1883, æt. 67 years, R. going to complete blindness, L. not so severe; had an attack of gastro-enteritis with some loss of blood two or three years before eyes failed. III, 4 living, good sight; III, 5 living but blind, probably of same disease; III, 6, æt. 73 years at record and quite blind; sight failed from the same disease at 65. IV, 1 æt. 33 years, good sight; IV, 3, æt. 31 years, nearly blind, age of onset not stated; is married.

Case 181*b*.* Higgens, *Lancet*, 1881, ii, p. 869.

Optic atrophy without other changes coming on in II, 4 at about 14½ and reducing V. to finger-counting in a few months; in II, 5 at 11½, and in II, 8 at 10. The disease set in in all three during about the first half of 1881. Mother showed evident signs of syphilis shortly before birth of



II, 4; she also had four or five miscarriages (*not marked on the diagram*, Fig. 181b) between II, 4 and 5; also II, 3 died at 14 months and II, 7 at 1 day old. II, 1, 2, 9, and 10 reported healthy. [If syphilis were the cause of the optic atrophy in these three siblings, why did the disease set in at approximately the same date (1881) in all of them? Was there some additional cause, such as lead poisoning or influenza?—E.N.]

Case 181*c*.* Suckling, *Lancet*, 1887, ii, p. 1271.

I, 1 became blind at 50. II, 1 went completely blind from double optic atrophy which came on gradually when he was 50; his sister, II, 2, was blind, and a female cousin (II, 3) on his mother's side is also quite blind (sex of I, 2 not given). No history of syphilis or disease of nervous system, and no signs of locomotor ataxy.

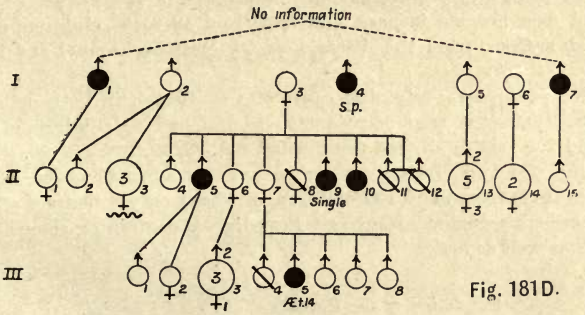


Fig. 181*d*. Unpublished. Case communicated by Mr. Jameson Evans (Birmingham).

No information about the ascendants of Gen. I. I, 1 to 7, five brothers, of whom three were affected, and two sisters, both of whom married and had children; one of them (I, 3) carried the disease, the other (I, 6), had only daughters, and therefore the point could not be determined. II, 4 to 12, nine children of I, 3, six male, of whom three are affected, three female of whom one (II, 8) died at 2; one of the survivors (II, 7) carries the disease, and the other (II, 6) has children of both sexes, none of whom have suffered hitherto (but their ages not stated). II, 11 and 12, twins, died at three months; III, 4 still-born; III, 5 æt. 14 years, affected; III, 6, 7, 8 have not reached the usually vulnerable age.

(*b*) *References to Cases of Leber's Disease Illustrating Various Statements in the Lecture.*

Recovery or marked improvement of sight is to be found in affected members of the following pedigrees: 77; one of either 83, 84, or 85; 87, 93, 49, 115, 116, 122, 132, 136, 141, 144, 160, 170, 171, 172; and in a few others.

"Anticipation" in Leber's Disease.

(i) In successive generations, the phenomenon is well shown in the following cases: 80, 49, 96, 108, 111, 112, 113, 50, 153, 154, 51, 168, 174.

Case 112, Despagnet, shows the anticipation in three generations, and in the case occurring in the third generation one eye recovered whilst the other passed into atrophy of the optic nerve.

(ii) Anticipation in successively born siblings, and occasionally in successive sibships of first cousins: 81, 88, 89, 91, 93, 49, 98, 99, 102, 105, 110, 45, 116, 117, 46, 132, 140, 144, 147, 113, 123, 181*a*, 150, 48, 156, 159, 171, 172, 175.

Transmission by Affected Males.

In six pedigrees containing only male cases of the disease 13 of the affected men became fathers, and had from 48 to 56 children, not one of which suffered from the disease, *viz.*, 45 omitting Gens. I and II, 120, 47, 168, 174, 167.

In five pedigrees containing cases of the disease in both males and females, 10 affected men became fathers and had 44 children, of whom 4 ♂ and 2 ♀, six in all, had the disease, *viz.*, 93, 49, 108, 142, 50.

Adding the two series together we have 23 affected males, who had between them from 92 to 100 children, of whom only 6 became affected, and these six occurred exclusively in pedigrees containing some affected females as well as males.

Condition of the Parents of Affected Females.

Both parents normal: 77, 78, 49, 95, 99, 105, 106, 112, 116, 119, 120, 141, 123. Father affected, 50 and 93 IV, 1; mother affected, 93 and 49.

Condition of the Children of Affected Females.

All the sons of an affected mother were affected in Cases 111, 138, and 146.

Some of the sons of an affected mother escaped in Cases 108, 142, 50, and 52.

Proportion of affected to normal in the total surviving issue of an affected mother and normal father, shown in 12 sibships of the following 9 pedigrees: 93, 49, 108, 116, 140, 50, 52, 51, 176.

Proportion of affected to normal in the total surviving issue of normal father, and mother normal but carrying the disease, shown in 38 sibships of the following 19 pedigrees: 92, 102, 105, 45, 115, 46, 120, 130, 144, 47, 148, 154, 48, 155, 168, 171, 174, 167.

Effect of Early Deaths upon the Proportion of the Survivors who suffer, in Childships originally consisting of Seven Children or more.

In the following 10 cases there were 12 sibships of 7 or more, with few, if any, early deaths, and one third of the individuals suffered from the disease.

Total births, 102, of whom 33 males and 3 females got the disease (36 in all): 110, 117, 130, 138, 142, 143, 47, 147, 158, 174.

In the following 16 cases, containing 18 sibships of 7 or more, a number of the children died early, and one half of the survivors suffered from the disease: 92, 93, 45, 115, 119, 120, 121, 140, 141, 144, 148, 154, 51, 162, 176, 167.

These 18 childships produced 195 children, of whom 96 died in infancy; of the 99 survivors 39 males and 7 females got the disease (46 in all).

Longevity of those Affected.

The following cases contain affected persons who lived to be 50 or more. Cases in which the disease set in after 40 in *males* are excluded. All cases in females who lived to 50 are counted, at whatever age the disease set in, as it has been supposed that the disease is especially likely to occur during the climacteric in women: 90, 103, 49, 111, 45, 116, 120, 140, 142, 50, 52, 154, 51, 161, 166, 168, 172, 176.

Early and Late Age of Onset.

(i) Cases in which the disease occurred early in life, *i. e.* from earliest childhood up to 13 years old: 92, 96, 95, 110, 116, 119, 141, 145, 50, 52, 149, 151, 153, 156, 171, 177, 178, 146; also two atypical cases, 181, 181*b*.

(ii) Cases in which the disease set in late, *i. e.* from 30 years old upwards.

A. Pedigrees showing examples of late onset in males:

(1) In the following only males were affected: 89, 90, 103, 107, 45, 46, 120, 136, 143, 47, 147, 168, 175.

(2) The following contained cases in both males and females: 93, 49, 111, 112, 141.

B. Pedigrees showing late onset in females: 80, 49, 95, 98, 106, 108, 110, 111, 113, 140, 141, 153, 51, 162, 176; also atypical cases, 181*a*, 181*c*.

Other affections, chiefly of the nervous system, in the stocks containing Leber's disease:—Epilepsy, Case 77, 98, 105, 120, 122, 138, 148; insanity or idiocy, 98, 173; mental defect, 45, in the only female (VI, 2) whose female ascendants went back to male with Leber's disease; severe hysteria, 115; diabetes, 95, 103; phthisis prevalent in 102, 98, 103; congenital colour-blindness, 106?, 117, 147.

The affected females are to be found in the following cases: 77, 78, 80, 93, 49, 95, 98, 99, 105, 106, 108, 110, 111, 112, 113, 116, 117, 119, 138, 140, 141, 142, 145, 50, 52, 123, 151, 153, 159, 51, 162, 165, 169, 176, 177, 178, 53; and in the following atypical cases: 181, 181*a*, 181*b*, 181*c*.

APPENDIX VII.

Nystagmus.

(*a*) Albinism.

(1) Under "Hereditary Nystagmus," allusion is made at p. cxxii *et seq.* of the Lecture to Albinism. With the exception of certain cases of nystagmus that I regard as a form of partial albinism and have already written about as such, the problem of albinism in general was not discussed in the Lecture since it forms the subject of a long and elaborate memoir planned and initiated some five years ago by Professor Karl Pearson, who has taken by far the largest share in its execution, although in certain sections Mr. C. H. Usher and I have been mainly responsible. This memoir is now very near completion, and may appear either a little before or a little after the present writing; although, therefore, any discussion of albinism as a whole in my Lecture would have been out of place, there is no impropriety in using a few of the pedigrees (somewhat condensed to save space) that will appear in the memoir to illustrate certain clinical features. Of course no general conclusions are to be drawn from these samples.

Fig. 53

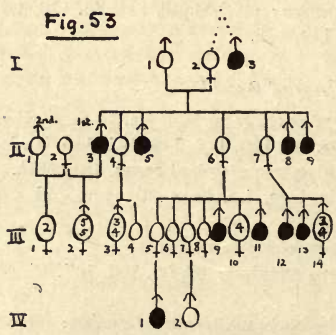


Fig. 56

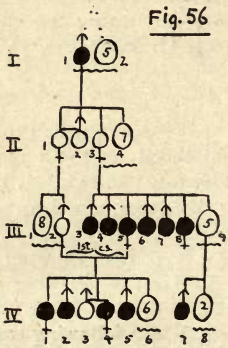


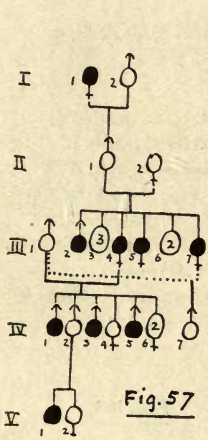
Fig. 53 illustrates the condition of incomplete albinism affecting chiefly the eyes, and is described at p. cxxiii of the Lecture. It is to be taken in

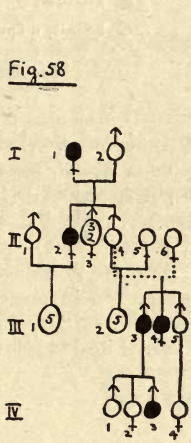
conjunction with Figs. 54 and 55, which, having been published, are inserted in the Lecture (p. cxxiv). (Fig. 53 is Fig. 295 in the forthcoming memoir upon albinism in man above mentioned, and is from a case sent by Mr. Jameson Evans, of Birmingham.)

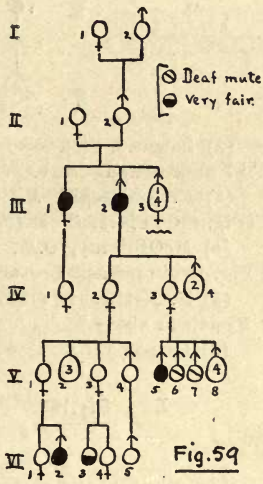
Fig. 56. General albinism with both discontinuous and continuous inheritance, the latter occurring where an albinotic woman marrying a normal first cousin of the same stock has albinotic children. Bisexual twins occur twice, and in one of them one member is an albino, the other normal. (Forthcoming memoir upon albinism in man, Fig. 27, Mr. C. H. Usher.)

Fig. 57. Discontinuous and continuous descent of albinism. No consanguinity. (*Ibid.*, Fig. 28, Mr. C. H. Usher.)

Fig. 58. Continuous and discontinuous descent. No consanguinity. A normal man of the albinotic stock marries twice, both wives being







from unrelated stocks; he has albinotic children by one wife, all normal children by the other. (*Ibid.*, Fig. 226, Dr. Schoute, Amsterdam).

Fig. 59. Discontinuous descent. Albinism and deaf-mutism in different members of same sibship. No history of deaf-mutism in any ascendants on either parental side (father's side not shown but inquiry made). No consanguinity. (*Ibid.*, Fig. 211, Mr. Wherry.)

Fig. 60. Marriage between two albinotic stocks that are believed to be unrelated, and between one of them and a third stock containing insanity and epilepsy, but no albinism. (*Ibid.*, Fig. 30, Mr. C. H. Usher.)

(2) The cases upon which the remarks on Hereditary Nystagmus in relation to Albinism at p. cxxv of the text of the lecture are based are as follows:

(1) Lloyd Owen, *O.R.*, i, p. 239 (1882), Fig. 54 in present Lecture. (Fig. 449 in forthcoming *Memoir on Albinism.*)

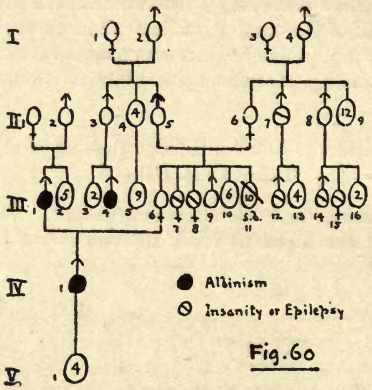


Fig. 60

(2) Lawford, *St. Thomas's Hospital Reports*, xvii, p. 166. Case 1. Fig. 187 in present Lecture. (Fig. 68 in *Memoir on Albinism.*)

(3) E. Nettleship, *R.L.O.H.*, ii, p. 366 (1887). Fig. 55 in Lecture. (Fig. 410 in *Memoir on Albinism.*)

(4) McGillivray, *O.R.*, xiv, p. 260 (1895). Case *B.* Gorrie family. Fig. 188 in present Lecture. (Fig. 448 in *Memoir on Albinism.*)

(5) E. Nettleship (1897). Fig. 186 in present Lecture. (Fig. 402 *Memoir* as above.)

(6) Caspar, *C.f.A.*, 1908, p. 199. Fig. 182 below.

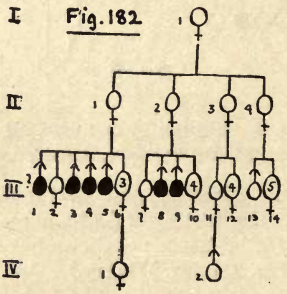


Fig. 182

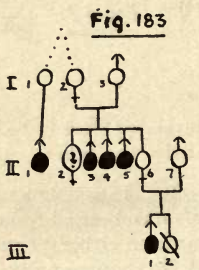


Fig. 183

In III are four childships, the first containing 4 males all affected and 4 females all free; second, 2 males both affected, 5 females free; third, 5 females free; fourth, 1 male and 5 females all free. Dr. Caspar has been unable to send any further information (February, 1909).

(7) E. N., unpublished, St. Thomas's Hospital out-patient, October 24th, 1881 (Simpson). (Fig. 183.)

III, 1, æt. 3½ years, fair complexion, choroid pale around O.D., but fundus normal, marked lateral nystagmus; healthy; did not have ophthalmia neonatorum; is thought by mother to be "short-sighted." Refraction not recorded. III, 2 treated for ophthalmia neonatorum at St. Thomas's; saw well, and had steady eyes; died of convulsions; no note of sex or colour of hair and eyes. II, 6 mother, æt. 22 years, normal eyes, some H., colour of hair and eyes not noted. Her 3 brothers and II, 1, a son of a sibling (I, 1) of her mother (I, 2) had moving eyes like III, 1; her sisters (II, 2), number not given, had steady eyes.

(8) Jameson Evans, Fig. 53 above described.

Fig. 188

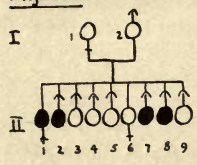


Fig. 186

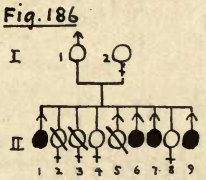
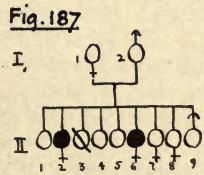


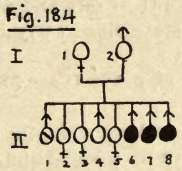
Fig. 187



(9) Dr. R. J. Smyth and E. Nettleship (1907). (Fig. 184.)

I, 1 and 2 lived to 70 and 65, not consanguineous; II, 1 operated by E. N. for glaucoma when 35; II, 2 died at 35; II, 3, 4 and 5 steady eyes; II, 6, 7 and 8 æt. 35, 32, and 30 years, nystagmus and more or less As., with defective vision ($\frac{6}{24}$ to $\frac{6}{12}$ corrected); irides of these 3 grey with

Fig. 184



pigment at sphincter circle; fundus not suggestive of albinism in any; II, 7 has reddish-brown hair which was lighter formerly. There are about 20 children in III, all said to have good sight and steady eyes (not shown in Figure).

The above 9 pedigrees contain 43 cases of nystagmus, 40 males, 3 females; and in the same childships about 65 to 70 normals, *viz.*, 20 males and 45 to 50 females, total 109 to 114.

(*b*) Day-blindness with Colour-blindness.

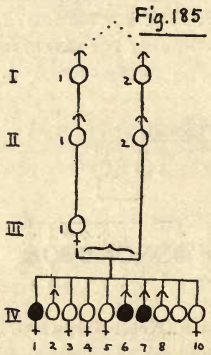
The family cases known to me are the following:

(1) Nettleship, *St. Thomas's Hospital Reports*, x, 1880. (Family 1, Foster.) Quoted in text of Lecture, p. cxxix, with Fig. 61.

(2) Nettleship, *ibid.* (Families 3 and 4, Pike, Channon.) *Ibid.*, with Fig. 62.

(3) Nettleship, *ibid.* (Family 6, Gould.) (Fig. 185.)

I, 1 and 2 brothers, reported to have seen well. III, 1 who was liable to melancholic attacks, but had good sight, married II, 2, her first cousin once removed, who also saw well, and had 9 children, of whom 8 were living at date of record, IV, 5 having died; IV, 1, æt. 34 years, not seen said to be affected in same way as her two brothers, IV, 6, æt. 25 years,



and IV, 7, æt. 23 years; both of these, with clear media, saw better in dull than in bright light, and were afraid of summer days and preferred to hold the head down to shade the eyes, in spite of having much contracted Fs. and retinitis pigmentosa; both colour-blind. They had nystagmus, and their sight, according to their own and their mother's account, had been in exactly the same state since early childhood. All the others said to have very good sight.

(4) Nettleship, *R.L.O.H.*, xi, p. 373 (Case 27), 1887. (Mr. Waren Tay's case.)

In a childship of 5, the first-born male, the other 4 female, the 2 elder girls (Nos. 2 and 3 born) totally colour-blind, day-blind, and amblyopic, V. with H. 3 D. corrected about $\frac{6}{24}$. Parents first cousins, but exactly how is not stated.

(5) Nettleship, *Ibid.* Case 28.

In a childship of 7, 1 of the 3 males and 1 of the 4 females affected; quite typically. H. 3 to 4 D. V. corrected $\frac{6}{24}$. No consanguinity.

(6) Nettleship, *Ibid.* Case 30.

In a childship of 4, Nos. 1 and 2, both female, typically affected; No. 3 female and No. 4 male, normal. Parents first cousins, but kind of cousinship not noted.

(7) Nettleship, unpublished, Joseph Thompson, 22 (*T.O.P.*, v, p. 7, 1885).

Parents normal, and not related by blood. Patient is second born of 8, all living, æt. from 24 to 2 years. His case is typical. The first born, male, 24, said to be similarly affected, and the youngest, female, 2,

thought to have same defect. Nos. 3 and 6 (males) and 4, 5 and 6 (females) all good sight. Interval of 8 years between No. 2 (patient, æt. 22 years) and No. 3 (æt. 14 years).

(8) 1897. Colburn (J. E.), *Amer. Journ. of Ophthalmology*, xiv, 1897, p. 237.

Nystagmus with total colour-blindness and V. about $\frac{6}{\frac{1}{2}}$ in a brother and sister of 14 and 12. Not albinotic. Very incompletely reported.

(9) Nettleship and Holmes Spicer, *T.O.S.*, xxviii, p. 83 (1908), with Fig. 63 in Lecture, p. cxxxi.

(10) Mr. Holmes Spicer and Dr. Souter, unpublished (1908), with Fig. 64, *ibid.*

The above 10 pedigrees contain 34 cases of this day-blindness with colour-blindness: 18 males, 15 females, and 1 sex not recorded. The same childships contain at least 45 (probably more) normals: 17 male, 22 female, and 6 or more sex unrecorded, total about 80 to 85.

The total of 84 cases mentioned at p. cxxix of the lecture is made up of my own and Grunert's series, including some single cases of mine not given above, but useful in relation to sex prevalence, and three others published since the appearance of Grunert's paper by Wehrli, 1903 (Abstract in Nagel's *Jahresbericht*, xxxiv, p. 92); Bjerrum, 1904 (Abstracted, *ibid.*, xxxv, p. 105, and again p. 205); Rönne, 1906 (abstracted *ibid.*, xxxvii, p. 78, and original reproduced in full in *K.M.f.A.* (Beiläge, heft), xliv, p. 193. In Bjerrum's case, two brothers of the (male) patient were also affected.

(*c*) Nystagmus, Unclassed.

The references to the fourteen unclassed cases of hereditary or family nystagmus, spoken of at p. cxxxii of the lecture, are given in chronological order below.

Published—

1892.* Wood (Casey A.), *The North American Practitioner*, April, p. 153.

1893.* Boulland, *Rec. d'Ophth.*, p. 569. This is an abstract by Rolland from the *Echo Médicale*, which appears to have copied from the original in the *Limousin Médical* of unspecified date.

1895.* MacGillivray (Angus), *O.R.*, xiv, p. 260. Case A (Neilson).

1895.* Audeoud, *Ann. d'Oculist*, cxiii, p. 412.

1895.* Burton-Fanning (F. W.), *The Lancet*, ii, p. 1497.

1898.* Morton (H. McI.), *Ophth. Rec.*, vii, p. 28.

1902.* Fisher (Theodore), *Brit. Med. Journ.*, September 6th.

1903.* Clarke (Ernest), *The Ophthalmoscope*, i, p. 86.

1903.* Hawthorne (C. O.), *Brit. Med. Journ.*, February 21st.

1903.* Sinclair (M. McIntyre), *ibid.*, May 23rd.

1908.* Dudley (W. H.), *A. of O.*, xxxvii, 565.

Unpublished—

1905. Case communicated by Dr. Angus MacGillivray (Dundee).

1906. Case communicated by Mr. Lawford (London).

1908. Case communicated by Dr. Vilhelm Magnus (Christiania).

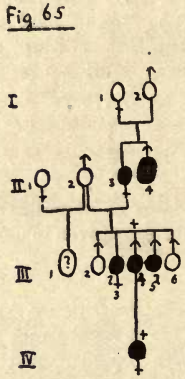
APPENDIX VIII.

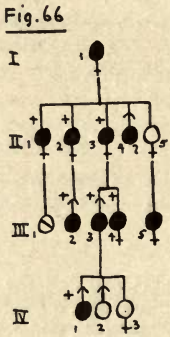
CORNEA.

Reticular and Nodular Keratitis.
Description of Figs. 65–69.

Fig. 65. Holmes Spicer, *T.O.S.*, xxiv, p. 42 (1904), and later information.

I, 1 believed to have had good eyes; I, 2 lived to 101, and is known to have had perfect sight to the end. II, 3, second wife of II, 2, and her brothers, II, 4 (number not recorded), said to have suffered in same way as III, 4 and his daughter. II, 2 and his first wife, II, 1, and her children, all had perfect eyes. III, 2, æt. 65 years at record, probably normal; III, 3 probably affected, sight "peculiar" in same way as III, 4, and an opera glass was useless to her; III, 4 seen by author, æt. 50 years, typical changes, eyes have been troublesome all his life; III, 5 had symptoms like those in III, 4, and on trying to enter the Navy failed to





pass the sight test, he died at 30; III, 6 has never had any trouble with his eyes. IV, 1, only child, seen by author at 23, characteristic changes, no severe symptoms, and V. with slight M. As. corrected $\frac{6}{6}$ and $\frac{6}{6}$ in R. and L., and appears to have been same for many years.

Fig. 66. Freund, *A.f.O.*, lvii, p. 377 (1904), and *Wien. klin. Woch.*, xix, No. 5, 1906. Family 2 (Hermann).

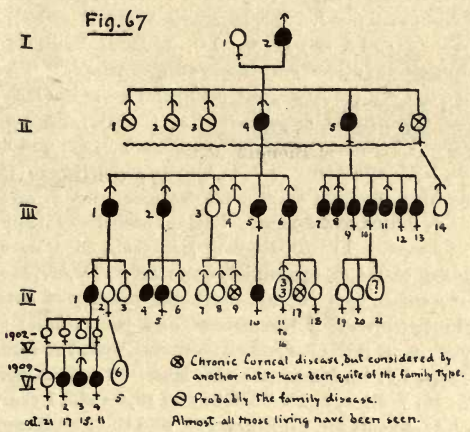
All marked "+" were examined by the author. The only ones believed, or known, not to have the family disease are II, 5, who died many years before the record; III, 1, who died at 23, and is said to have had "scrofulous inflammation of the eyes"; and IV, 2 and 3, æt. 10 and 6 years at record, and definitely stated by the author to have been free from the disease at that time; though not starred they were probably

examined. The ages of the affected ones when seen were: II, 1 (author's Case 8) 61, II, 2 (Case 9) 56, III, 2 (Case 10) 26, III, 3 (Case 12) 39, III, 4 (Case 14) 38, IV, 1 (Case 13) 13, III, 5 (not seen, Case 15), 26. In II, 3 (Case 11), age not stated, the eye disease had existed more than twenty years. II, 4 not seen or described, but stated to be affected; was 46 at date of record. Nothing said about early deaths.

Fig. 67. Freund, *ibid.*, Family 1, Bienert.

In this genealogy the ages, unless otherwise stated, are as given in the author's earlier publication (*A.f.O.*, lvii), and refer apparently to 1902, or sometimes perhaps rather earlier. The pedigree now presented in Fig. 67 is the result of collating the published ones of 1904 and 1906, and adding important new information that Dr. Freund has with the greatest courtesy supplied to me in reply to questions.

Dr. Freund's latest reply, dated June 14th, 1909, three days after the delivery of the lecture, gives the result of his examination of the eight children IV, 10 to 18; whilst in a letter of May 3rd he gave the present



condition of the four siblings, V, 1 to 4, who were all normal seven years ago, whilst three of them now show the typical condition. I reproduce the names of all the members as given by Dr. Freund in order to facilitate reference if still further information should be forthcoming in future. I, 1 died young, had good eyes. I, 2, Wenzel Bienert, husband of I, 1, also died young, between 1860 and 1870; is reported to have had the family disease. II, 1, 2, 3, order of birth not recorded, died before Karl (II, 4); all three had bad eyes, the eldest being quite blind, no other details. II, 4, Karl Bienert (the elder), died in 1889, age not given; reported to have had the family disease; his place in

* Gen. VI, 1909, should be V. The same childship was examined in 1902 and again in 1909.—E. N.

the childship not given. II, 6, æt. 84 years at date of first record, and still living (May, 1909); eyes affected for more than fifty years; the corneæ are densely opaque and scarred, and it cannot now be proved that she has the family disease; her only child, Daniel, æt. 56 years (III, 14) has normal eyes. II, 5, Karoline Wolf, æt. 72 years and still living (May, 1909), has had the family disease all her life. III, 1, Karl Bienert (the younger), 63, has had the corneal disease thirty years. III, 2, Ferdinand Bienert (the elder), died at 36 in 1876; had the family disease and his sight was very bad. III, 3, Josef Bienert, 53, corneæ clear but iris shows remains of fœtal pupillary membrane. III, 4, Edward Bienert, died at 30 in 1879, believed to have had good sight. III, 5, Antoine Bartosch, 49, and III, 6, Johann Bienert, 48, both typically affected. III, 7, Wenzel Wolf, 50, affected, but sight still relatively good. III, 8, Ant. Wolf, 48, affected and sight very bad. III, 9, Karoline Beer, died at 43 between 1890 and 1900, was affected by the family disease, but is said to have still seen well. III, 10, Berta Jung, 45, affected and sight very bad. III, 11, Leopold Wollmann, 41, affected and sight very bad. III, 12, Matilda Rösler, 39, affected, but sight still good. III, 13, Marie Wolf, 17 (? 37), affected, and sight very bad. III, 14, see II, 6. IV, 1, Emil Bienert, 39, affected. IV, 2, Frau Engelfeld, about one year younger than IV, 1, reported to be normal, as also her six children, but could not be seen (May, 1909). IV, 3, Karl Bienert (the third), examined at 13 (? 1900), high myopia but no corneal disease. IV, 4, Karl Bienert (the fourth), 31, and his sister, IV, 5, Auguste, 29, both affected. IV, 6, Ferdinand Bienert (the younger), 26, moderately high myopia, no corneal changes. IV, 7 and 8 examined and normal; IV, 9 died at 24 nearly blind, but believed not to have had the "Bienert disease." IV, 10, Hedwig Bartosch, 23, affected. IV, 11 to 18, eight children of III, 6, examined, June 1909; IV, 17, Max Bienert, 5, "already shows small, spotted, sub-epithelial opacity of both corneæ; it extends to the periphery of the cornea, and the corneal surface is at present smooth; it is not altogether identical with the family disease." The other seven, IV, 11, Marie, 20; 12, Hans, 19; 13, Eleonore, 17; 14, Margarete, 11; 15, Walter, 9; 16, Curt, 8; and 18, Gerda, 1 year, are normal. IV, 19 to 21, Karoline Jung, 26, Emma. 11, and their siblings, no information obtainable. V, 1 to 4, examined in 1902 and again in May, 1909: V, 1, Mathilde Bienert, 14, normal, and is still normal in May, 1909, æt. 21 years; V, 2, first seen at 10 with normal corneæ; when re-examined at 17 (May 1st, 1909) characteristic changes in the corneæ; the same is true of V, 3, normal when seen at 8, the same corneal changes at 15; and of V, 4, normal at 4 and characteristically diseased at 11. In the figure Gen. VI, 1909, should have been V.

Fig. 68. Doyne and Stephenson, *The Ophthalmoscope*, iii, 213 (1905).

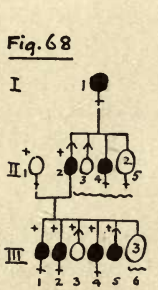
I, 1, eyes bad from youth, and towards end of life sight so bad that she had to be led about; died at 65. II, 2 seen at 48, with very advanced opacity of R., and less of L.; age of onset 39, or perhaps earlier. II, 4, a sister, now dead, said to have had the family disease.

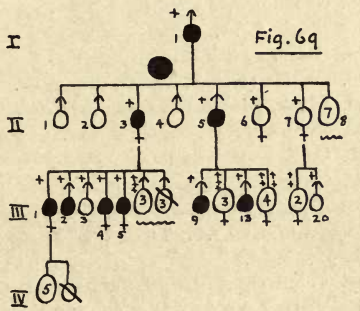
III, 1, æt. 24 years, eyes began to fail at about 16, but with interval of three years between R. and L.; now almost universal dense opacity; III, 2 began at 9, now 22, and as bad as III, 1; III, 4 disease began at 7 and has steadily got worse, and now, at 15, is nearly as bad as III, 2, and has much severe acne on face*; III, 5 began at about 11, seen at 12; chief part of opacity showed much resemblance to "transverse calcareous film," and, as is common in that condition, showed numerous small, clear holes. No consanguinity.

Case 68*a*. A new case has been given to me this year by Mr. Herbert Fisher, but as there has not yet been an opportunity for examining all the available members of the family I withhold it; at least two sisters are affected, and probably two or three of their siblings.

Fig. 69. Folker, *T.O.S.*, xxix, p. 42 (1909).

I, 1 now 92, history of first failure when about 50; about ten years later





operated for cataract in both eyes; wife living, has had 13 or 14 children, 7 still living, and no miscarriages. II, 3, now 50, sight "always" been defective; 11 children, 8 living, 3 died under 2 years; II, 5, æt. 46 years, sight "always" been defective; has 9 children. III, 1, æt. 30 years, sight defective as long as she can remember, and apparently getting steadily worse after each confinement; has had 6 children in 8 years, one dying in infancy, 5 living; III, 2, æt. 28 years, sight defective all his life, now V. $\frac{6}{18}$; III, 4, æt. 21 years, sight defective as long as she can remember, now V. $\frac{6}{18}$, married, 1 child, æt. 10 weeks; III, 5, æt. 18 years, no definite history of commencement, but is getting worse, V. $\frac{6}{12}$; III, 9, æt. 21 years, has never noticed any defect of sight, and has now $\frac{6}{6}$ in R., $\frac{6}{9}$ in L., but central area of each cornea shows 20 to 30 small scattered spots; III, 13, æt. 12 years, no symptoms, and V. $\frac{6}{6}$ with each eye, but has a few small dots of corneal opacity like his brother.

A general review of the disease illustrated by these pedigrees leaves one in no doubt that it is often, if not always, progressive, that in an early stage sight may be so little affected that nothing short of careful

* Severe scar-leaving acne was observed by Marcus Gunn in one of his cases: *T.O.S.*, xix, p. 97.

examination of the corneæ can be taken as conclusive, and that practical blindness may ensue from gradual extension of the area and increase in the density of the opacity. Careful inquiry in many of the cases has shown that there is no reason whatever for thinking that syphilis takes any part in causing the disease.

The following is a list of the principal papers upon nodular and reticular opacity of the cornea. * Most important. Some others may be found at end of the article by Doyne and Stephenson.

*1890. Biber, *Inaug. Dissert.*, Zurich.
*1890. Groenouw, *A. of O.*, xix, p. 245.
1891. Chevallereau, *France Médicale*, May 2nd.
1891. Manz, *Wien. med. Woch.*, Nos. 3 and 4.
1892. Oliver (C. A.), *Amer. Journ. of Ophth.*, p. 234; also given in *O.R.*, ii, p. 349 (same year.
1893. Eversbuch, *Deutsche med. Woch.*, No. 41.
*1898. Groenouw, *A.f.O.*, 46, i, p. 85.
*1899. Haab, *Z.f.A.*, ii.
*1899. Dimmer, *ibid.*, ii.
*1899. Collins (E. T.), *T.O.S.*, xix, p. 30.
1899. Block, *Niederländ Ophth. Gesellsch.*, December 10th.
*1902. Fuchs, *A.f.O.*, 53, iii, p. 423.
*1902. Collins (E. T.), *T.O.S.*, xxii, p. 148.
*1902. Gunn, *T.O.S.*, xxii, p. 97.
1903. Hess, *A.f.O.*, p. 378.
*1904. Freund, *A.f.O.*, lvii, p. 377; also (*1906) *Wien. klin. Woch.*, xix, No. 5.
1904. Fehr., *C.f.A.*, xxviii, January and June.
*1904. Veasey (C. A.), *A. of* O., xxxiii, p. 510.
*1904. Spicer (T. Holmes), *T.O.S.*, xxiv, p. 42.
1904. Deutschmann, *Beitr. z. Augenheilk.*, H. 61, p. 14 (1904).
*1905. Doyne and Stephenson, *The Ophthalmoscope*, iii, p. 213.
*1908. Hudson, *T.O.S.*, xxix, p. 11.
*1908. Folker (H. H.), *T.O.S.*, xxix, p. 42.

APPENDIX IX.

Abbreviations of Titles of Periodical Publications.

A.f.O.—Von Graefe's *Archiv für Ophthalmologie.*
K.M.f.A.—Zehender's *Klinische Monatsblätter für Augenheilkunde.*
R.L.O.H.—*Royal London (Moorfields) Ophthalmic Hospital Reports.*
T.A.O.S.—*Transactions of the American Ophthalmological Society.*
T.O.S.—*Transactions of the Ophthalmological Society of the United Kingdom.*
C.f.A.—Hirschberg's *Centralblatt für praktische Augenheilkunde.*
A. of O.—Knapp's *Archives of Ophthalmology.*
O.R.—*Ophthalmic Review.*

ADLARD AND SON, IMPR., LONDON AND DORKING.